Multimodality Monitoring in Paediatric Severe Traumatic Brain Injury: The Contributions of Brain Oxygen, Transcranial Doppler and Autoregulation Monitoring to Conventional Methods of Monitoring

by

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Abstract

Traumatic brain injury (TBI) is a highly complex clinical condition in the most complex organ of the body. The foundation of care of the patient with severe TBI is the prevention of secondary insults to the brain. This relies on conventional monitoring tools to identify patients at risk, but often these may fail to detect important secondary insults. Moreover, the therapies that are used commonly in the critical care environment all have potential adverse effects, many of which may not be evident. TBI treatment in children is further complicated by changing thresholds with age, and the much smaller evidence base compared to their adult counterparts.

Although it is clear that our current tools for monitoring the brain are suboptimal, the benefit of additional bedside techniques for monitoring and management of children with severe TBI is uncertain. Therefore, the aim of this study was to evaluate the potential impact of brain tissue oxygen tension (PbtO2) monitoring, Transcranial Doppler (TCD) Monitoring and the assessment of cerebrovascular autoregulation on 1) our understanding of the pathophysiology of severe TBI in children, and 2) the detection of secondary insults and its impact on management.

A prospective observational study was undertaken of children with severe TBI who underwent monitoring over a 2 year period at the Red Cross War Memorial Children's Hospital. The main cohort of these patients underwent PbtO2 monitoring in addition to conventional intracranial pressure (ICP) and cerebral perfusion pressure (CPP) monitoring. In addition to these, selected patients also underwent TCD studies and testing of cerebrovascular autoregulation to aid management. Clinical, demographic and outcome data were examined for associations with more than 5000 hours of physiological data recordings of continuous variables. Detailed statistics were performed to answer specific questions related to the associations of these monitored variables with other clinical factors, treatment options, and outcome.

The main findings were:

1. Episodes of critically low PbtO2 were very common after severe TBI, and often occurred despite adherence to recommended conventional treatment targets.
2. Clinical and other physiological factors have a variable relationship with brain hypoxic-ischaemic episodes.
3. Low PbtO2 independently predicts poor outcome, mortality and the development of delayed infarction in children.
4. Acute admission grading systems used for prognostication do not necessarily predict the risk of secondary injury.
5. PbtO2 monitoring may be used to assess the influence of therapies on intracranial dynamics. In this work, the effects of ICP reduction, blood transfusion and normobaric hyperoxia on PbtO2 were separately evaluated, producing novel results.
6. TCD-monitored flow velocities have associations with ICP and PbtO2, but show a wide variability which emphasizes the major differences between individual patients.
7. Bedside determination of autoregulation with TCD is feasible in children with TBI. Impaired autoregulation is common and the status of autoregulation is associated with clinically important changes in ICP and PbtO2 in response to a change in blood pressure.

In summary, this is the largest work yet on PbtO2 monitoring in children with severe TBI, and the first to examine PbtO2 in combination with other physiological variables, most notably TCD flow velocities and the status of autoregulation. The work presents new findings that 1) contribute to our understanding of the pathophysiology of childhood TBI, 2) emphasise the heterogeneity of patients with TBI, and 3) suggest that complementary modalities of monitoring provide a better understanding of the challenges in an individual patient that may help tailor therapy appropriately to improve outcome after severe TBI.

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Foreword

The brain is astonishingly complex; therefore, it is entirely expected that the task of caring for a patient who has an acute brain injury, particular a child, should be an enormous challenge that leaves the clinician feeling inadequate for the task at hand. The tools we have at our disposal seem blunt at best and often we are left with a sense that we are fumbling around in the dark while trying to manage a patient with severe impairment of many of the physiological mechanisms that usually protect the brain. The final complex model we are faced with results from an interplay between multiple variables, the product of which is unique to the individual. Therefore, I am of the belief, as are many others, that a rational approach to this challenge is to take as much information available from the patient to best enable us for the task of managing an individual.

This is my approach to this thesis. Although not as equipped as many other units in the world may be with access to other forms of technology, we have sought to use what we have available to best understand how we can manage patients better. Because of the complexity of brain injury, any work that seeks to look at multiple aspects of the injured brain, and the way that these inter-relate, runs a risk of lack of cohesion. As best as possible I have attempted to focus on practical approaches to examining the disturbance of brain physiology that can potentially guide management in a working ICU, and demonstrate the relevance of each to helping us achieve our goal, even in the context of the developing world.

Structure of the Thesis

The thesis is divided into two main sections. **Section A: Background** is structured to provide a background to the study. It summarises important concepts in epidemiology and clinical aspects of paediatric severe TBI, and the practical techniques based on the principles of monitoring disturbances in brain physiology. The focus in this latter part is on TCD, autoregulation and PbtO2 monitoring that serves as a background to the following section.

Section B: Patient Studies examines specific questions related to these monitoring strategies in children with severe TBI admitted to the Red Cross War Memorial Children's Hospital in Cape Town. The research took the form of a prospective observational study of patients managed during this period. The main cohort of patients is 52 children who underwent monitoring for ICP, CPP and PbtO2 between June 2006 and May 2008. A subgroup within this cohort also underwent TCD studies and autoregulation monitoring. All interventions during this period were part of our clinical protocol for managing patients with TBI and were independent of the purposes of the study. The section is divided into a number of parts, each of which represents a discrete observational study. Because analyses of results for different sections were performed at varying time points, some of the numbers of children included varied accordingly. Where this is the case, the number of patients included and the time periods over which they were studied are specified.

The purpose of each of the chapters in Section B is to demonstrate some of the complex ways in which clinical, physiological and treatment factors interact with each other and with outcome. It is the hope that better understanding of these relationships, and the development of better ways to detect and monitor them, will lead not only to the benefit of an individual patient, which is always the prinicipal goal, but also to renewed enthusiasm among clinicians who have lost some of the drive to grasp the challenge of aggressively managing a patient with a head injury.

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Section B: Patient Studies

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Abbreviations

AR	Autoregulation
ARI	Autoregulatory Index
BP, SBP	Blood pressure, systolic blood pressure
CBF	Cerebral blood flow
CI	Confidence Interval
CPP	Cerebral Perfusion Pressure
CSF	Cerebrospinal fluid
CT	Computed tomography scan
DCH	Decompressive craniectomy
DCI	Delayed Cerebral Infarction
EEG	Electroencephalography
FiO2	Inspired fraction of oxygen
FV	Flow velocity
FV_{MCA}	Flow Velocity in the middle cerebral artery
GCS	Glasgow Coma Scale
GEE	General estimating equation
GOS	Glasgow Outcome Score
Hb	Haemoglobin
ICP	Intracranial Pressure
IQR	Interquartile range
LME	Linear effects regression model
MAP	Mean Arterial Pressure
MCA	Middle Cerebral Artery
MRI	Magnetic Resonance Imaging
MVA	Motor vehicle accident
NAI	Non-accidental injury (shaken baby syndrome)
NIRS	Near-infrared Spectroscopy
PaCO2	Partial pressure of arterial carbon dioxide
PaO2	Partial pressure of arterial oxygen
PbtO2	Brain tissue oxygen tension

PCPCS	Paediatric Cerebral Performance Category Scale
PET	Positron Emission Tomography
PI	Pulsatility Index
PICU	Paediatric Intensive Care Unit
PIM2	Pediatric Risk of Mortality Score
PTCI	Post-traumatic Cerebral Infarction
PTS	Pediatric Trauma Score
RBCT	Red Blood Cell Transfusion
SaO2	Pulse oximetry
SJVO2	Jugular Bulb Venous Saturation
TBI	Traumatic Brain Injury
TCD	Transcranial Doppler

Definitions

Severe TBI	TBI with GCS of ≤ 8
Hypoxia	PaO2<60mmHg or SaO2<90%
Hypotension	Systolic BP <90mmHg
Elevated ICP	ICP > 20mmHg

Section A

Chapter 1

Epidemiology and Outcome in Paediatric Severe TBI

The Burden of Disease

TBI is a major contributor to the global burden of disease. Overall, injury is the leading cause of death for children and adults between the ages of 1 and 34 years old in the United States [20, 320] and accounts for more than two thirds of the deaths in children between 5 and 19 years old [55]. In children and young adults more lives are lost due to injury than all the other causes of death combined [226, 320], and even up to age 65 injury remains the leading contributor to years of potential life lost. The situation in developing countries is even more concerning. Even though infectious diseases are an important cause of loss of life, the overall burden of paediatric trauma is usually higher than in the developed world, and is driven by injuries related to road traffic accidents and violence. In South Africa, for example, injury is the leading cause of death in young adults and children over the age of 4 years [38], which is not too dissimilar to that of the United States and Europe. However, the overall burden of trauma is much higher. When compared with equivalent data from the United States, the increased risk of injury in South Africa is stark – the chances of dying due to injury in childhood (age 5-15 years old) are more than 6-fold greater in South Africa [38, 189].

Of all injured children, those who sustain TBI have the highest chance of dying or being permanently disabled [50, 185, 363]. TBI has been implicated in as much as 70-80% of accidental deaths after trauma in children [185, 230]. This is important because these injuries are at least preventable; therefore, injury prevention programmes are important. But even once TBI has been sustained, the high incidence of death and severe disability may still be ameliorated by access to effective emergency care. Early

initiation of treatment to prevent prehospital insults may contribute to the avoidance of as much as 30% of paediatric deaths [328]. Also, more aggressive treatment of paediatric TBI appears to have improved outcome in the last decade [51, 105, 370]. However, the hospitalization rates for TBI are increasing and children in lower income countries, and the uninsured in higher income countries, appear to be at highest risk of poor outcomes [37, 38, 86, 321, 322, 370]. However, when considering the overall contribution of injury to the burden of disease, deaths alone represent only the tip of the injury pyramid. For each injury death, there are 200 emergency department visits [320] and many children may be left with some permanent neurological or physical disabilities that have far-reaching implications for the immediate family and wider community. Furthermore, the economic costs of injuries are considerable. For example, the direct and indirect injury costs of motor vehicle accidents alone were $146 billion in the United States for the year 2000 [320].

Demographic Profiles of TBI in Childhood

In many studies the definition of childhood varies. This influences the reported demographic characteristics of the population, their physiological profiles, and also probably the reported outcome. Some studies include patients 18-21 years old [134, 309, 371] in their reports of paediatric patients. In the present report, only children less than 15 years old are included. The age range included in a paediatric study is important because the mechanisms of injury differ and the physiology of older adolescents may be more similar to that of adults than younger children. Many of the physiological thresholds used in the management of older adolescents in the intensive care unit are similar to or the same as those used in adult patients.

In all series of paediatric severe TBI, boys are more often injured than girls [363]. The common mechanisms of injury depend on the severity of the head injury, the age group, and the economic background [86]; therefore, significant variations in the relative proportions of mechanisms of injury are reported [363]. Minor falls are common in mild TBI. Severe TBI in young children is likely to be due to significant falls from a height and non-accidental injury, while older children are more likely to be

injured in motor vehicle accidents. In reports that include older adolescents, assault becomes more common, but this is rare in true paediatric series for most reports from developed world settings. In a different economic milieu though, blunt and penetrating assault in children is reported with greater frequency. Although these assaults are not accidental injuries, the formal term non-accidental injury (NAI) will be reserved in this report for the typical shaken baby syndrome that has been extensively described [101].

Outcome after Paediatric Severe TBI

Mortality

A wide range of mortality has been reported for severe TBI in children, from 9% to 57% [44, 50, 66, 109, 321, 405, 412]. On average, these studies of paediatric severe TBI report a mortality rate of 20-30%. Severe disability is reported in 30-50% of survivours [109, 411]. A number of factors influence these reported rates, including 1) publishing bias toward more favourable outcome, 2) types of injury included in the series, 3) injury severity, 4) selection criteria for the series (for example, most reports exclude patients presenting with brain death), 5) quality of pre-hospital care, and 6) quality of care in the hospital setting.

Bruce et al reported a very low mortality rate of 9% for children with severe TBI [44]. This particular report generated controversy as the authors suggested that a mortality rate of less than 10% should be expected in a paediatric trauma hospital, yet these results were not easily replicated elsewhere. Johnson and Krisnamurthy fuelled the debate in their response to this article by reporting a large series of 4041 children from 5 Level 1 trauma centres [167]. The overall mortality rate in their study was 36.5%, and none of the hospitals reported a mortality rate less than 30%. For patients referred indirectly (via a local hospital) this figure rose to 50%. However, the subject remains contentious [205].

Age and outcome

Better outcomes after TBI in children compared with adults are often reported [206, 363]. For example, Luerssen et al found a significantly lower mortality rate in a cohort of 1906 children compared with adults [206]. However, there are a number of important factors that should be taken into account when interpreting these results. First, adult series usually include elderly patients, who are known to have a significantly higher mortality rate than younger adults [144, 377, 414]. To illustrate this point, Hukkelhoven et al reported that the Odd's ratio for poor outcome in adults increases by 40-50% per 10 years of age, independently of the presence of risk factors [157]. Second, the spectrum of injury is different between adult and paediatric TBI. For example, adults are more likely than children to suffer TBI as a result of penetrating injury. When mechanism of injury is taken into account, the mortality rate for children with severe TBI appears to be similar to that of adults [167]. Third, although plasticity of the developing brain is often touted as a significant advantage for recovery after TBI, there is mounting evidence of the unique vulnerability of the developing brain [18, 122, 123, 413]. What is clear though is that within the paediatric group, young age is a risk factor for poor outcome [10, 99, 120, 206, 274]. In children, increasing age is associated with improved outcome, while the reverse is found in adults [258].

Finally, the assessment of disability in children is more challenging. Adults have a stable pre-injury level of functioning that be used as a baseline for comparison when outcome is evaluated. Children, on the other hand, are rapidly developing; therefore, recovery to a pre-injury baseline is not a useful endpoint [122]. Furthermore, their pre-injury level of functioning is influenced by economic background and level of schooling. Therefore, optimal evaluation of outcome in children to detect disability requires specialised tools not usually available to most clinicians [231]. Even after apparently mild TBI in childhood, long term chronic sequelae may develop that are often overlooked [143].

Should children be treated at specialised paediatric trauma centres?

The issue of the optimal infrastructure for paediatric trauma is an important one. Most paediatric trauma cases are managed in nontrauma centres [357] and some may even receive definitive treatment

at adult hospitals. Some authors contended that children with severe injuries are best managed at a dedicated paediatric hospital with trauma experience or accreditation [138, 357]. Their arguments centre on the physical and physiological differences in children compared to adults; therefore the infrastructure required for managing a severely ill child, including the availability of specialised equipment and experienced clinicians, is best found at these hospitals. On the other hand, the advantage of managing larger volumes at adult hospitals may offset the advantages of dedicated, but smaller, paediatric trauma centres. The relative benefits of each have been difficult to demonstrate in the literature, but the weight of current outcomes-based evidence does appear to favour the management of children at dedicated paediatric trauma centres [357].

Chapter 2

Clinical Aspects of Paediatric Severe TBI

The Glasgow Coma Scale: Assessment and Association with Outcome

The GCS has long been used for the assessment of the level of consciousness in TBI and prediction of outcome. In children, the utility of the GCS is limited in younger age groups, particularly the preverbal child. Therefore, alternatives to the GCS have been proposed, including the Pediatric Coma Scale [335, 336] and the Children's Coma Scale [135]. However, all scales that assess the level of consciousness may be limited by prehospital sedation; therefore, they may be misleading in predicting outcome, particularly when used for trials of TBI [24, 354]. However, the postresuscitation GCS remains the standard for triage of patients and its association with outcome in paediatric TBI has been consistently reported [50, 66, 99, 109, 134, 274, 308].

Pupils

Pupil reactivity to light is associated with outcome after TBI. Unilateral and bilateral pupil abnormalities have been associated with increased mortality and disability in survivors [134, 223, 274, 280, 390]. Unilateral pupil abnormalities may be associated with raised ICP and impending transtentorial herniation, while bilateral non-reactive pupils may be associated with impending brainstem death. Both may be related to brainstem ischaemia. From an analysis of patients in the Traumatic Coma Database [223], 47% of patients with a unilateral unreactive pupil, and 82% of patients with bilaterally unreactive pupils were dead or in a vegetative state at discharge. The association between pupillary abnormalities and compression of the mesencephalic cisterns on head CT is also clear. Van Dongen et al [390] showed that 75% of patients with complete obliteration of the cisterns also had unilateral or bilateral pupillary abnormalities. A combination of criteria that included CT findings (state of cisterns and brain

parenchymal lesions) and clinical findings (motor score, pupil abnormalities and age) correctly predicted outcome in 96% of their cases.

The Role of Prehospital Hypotension and Hypoxia

Incidence: Prehospital hypotension and hypoxia are common in paediatric TBI. Chiarreti et al [66] reported hypoxia and/or hypotension in 68% and Ducrocq et al [99] reported hypotension in 31% in their respective series of children with severe TBI. The true incidence of hypotension in particular, though, is uncertain because the definition of hypotension in paediatric TBI varies between reports. Many studies report prehospital BP in children compared to an absolute systolic BP less than 90mmHg, but others suggest that systolic BP less than the 5th centile for age is a better predictor for outcome [71]. Few studies report BP in relation to MAP thresholds, which is important because MAP is a better reflection of CPP. Also, in children height is an important factor influencing the normal range of BP, but is seldom considered. Height is related to BP independently of age [136, 299]. It is an indicator of physiologic maturity and is better correlated with skeletal age than chronologic age.

Relationship with outcome: Studies in adults and children report worse outcome if a patient experiences an episode of hypotension or hypoxia in the prehospital period. In adults, hypotension occurs in more than a third of patients and is associated with a 150% increase in mortality [64]. In children, the adverse effects of hypotension and hypoxia are also consistently reported [65, 66, 99, 134, 273]. Pigula et al evaluated mortality in 58 head-injured children from an institutional series and 451 from the National Paediatric Trauma Registry to assess the impact of hypoxia and hypotension on outcome, using a systolic BP < 90 mmHg to define hypotension and PaO2 < 60 mmHg to define hypoxia, and found a mortality rate of 67% for patients who had experienced hypotension and/or hypoxia versus 16% for children with neither insult [273]. They also found that hypotension was more predictive of mortality than hypoxia. However, it remains uncertain whether this close relationship between prehospital insults and poor outcome reflects the association of both with increased severity

of injury or whether it represents a modifiable endpoint that can improve outcome if corrected or avoided.

Polytrauma

Severe diffuse brain injury in children is usually associated with MVAs; therefore many children present with polytrauma. Approximately half of all children who present with severe TBI have polytrauma [109, 134]. The addition of extracranial injury increases the incidence of hypotension and hypoxia and is usually associated with worse outcomes [363], although this is not always a consistent finding [109]. Given their relatively large head size and poorly developed neck muscles and ligaments children are at risk of significant cervical injuries [266], and in particular, of Spinal Cord Injury Without Radiographic Abnormality (SCIWORA) [270]. The range of neurological abnormalities broadly correlates with the MRI images and varies from mild or transient neurological disturbances (with a normal cord, edema or minor haemorrhage) to permanent deficits (with cord transection). In consideration of the difficulties in paediatrics of emergency airway management, complex resuscitation, chest and abdominal trauma, unique orthopaedic requirements and different ventilatory strategies, the child with multiple injuries is probably best managed in a dedicated paediatric trauma centre with a paediatric ICU [107, 357].

CT imaging and outcome

Unlike adult TBI, diffuse injury is proportionally more common in children with severe TBI [42, 274]; mass lesions requiring surgical removal are less common in children. Diffuse brain swelling has been reported to be the commonest CT finding in children with severe TBI [43, 109, 198] and appears to increase the likelihood of poor outcome [13, 109, 274]. These patients may have mortality rates well over 50% [13, 274]. The association between subarachnoid haemorrhage on head CT head and poor outcome in paediatric TBI has also been reported [274].

The most widely used head CT-based classification of TBI is that proposed by Marshall et al [223], in which there are 6 categories. Briefly, these include: Diffuse injury I (no visible pathology), Diffuse Injury II (cisterns present, midline shift<5mm), Diffuse Injury III (cisterns compressed or absent, midline shift<5mm), Diffuse Injury IV (midline shift >5mm); evacuated mass lesion (any lesion surgically evacuated), and non-evacuated mass lesion (lesion>25cc not surgically evacuated). The highest mortality reported in this paper occurred in the Diffuse Injury IV and non-evacuated mass lesion categories (and brainstem injuries). However, there are potential limitations of this classification [208]. The diffuse injuries and mass lesions are separated in categories, whereas in reality they often occur concurrently. Also, mass lesion type is not specified. For example, subdural and epidural haematomas have different outcomes but this is not reflected in the classification. However, all CT-based classifications have limitations and the Marshall classification continues to be widely used.

The association of CT-based criteria and ICP is variable. In the original description of the Marshall classification, there was an association with elevation ICP, but others have not always found this [144]. Also, one third of patients with severe TBI and normal initial CT head scans may go on to develop increased ICP [203]. Others have confirmed the risk of increased ICP with normal CT scans [152].

MRI is more sensitive than CT scanning for detecting brain injury, particularly for the detection of diffuse axonal injury and white matter lesions, and may be more accurate for predicting outcome [108, 199, 241]; however, its use is generally impractical in the acute phase and does not necessarily alter management.

Chapter 3

Intracranial Pressure Monitoring in Paediatric Severe TBI

Aetiology of Elevated ICP in TBI

Elevated ICP after TBI may occur as a result of intracranial haematomas, cellular oedema, vasogenic oedema, venous congestion, hydrocephalus and seizures. Vasogenic oedema occurs after mechanical microvascular tissue disruption, which results in breakdown of the blood-brain barrier and increased vessel permeability with accumulation of water in the interstitial spaces. The process is mediated by various compounds such as bradykinin, arachdonic acid, histamine and free radicals. Cellular oedema on the other hand, results from ischaemic injury and the failure of cellular energy metabolism, although there is probably also a neurotoxic pathway that occurs in the absence of ischaemia as a consequence of ionic disruption [221]. The extracellular-intracellular sodium gradient is disrupted, leading to the influx of water into the cells. Recent evidence suggests that cellular oedema is more prominent after head injury than vasogenic oedema or vascular engorgement [222].

Cerebral hyperaemia causes brain swelling due to engorgement of the vascular bed secondary to a vasoreactive event, the mechanisms for which are unclear. The diagnosis is not straightforward; areas of hyperaemia do not necessarily correlate with abnormal areas on MRI scans [307]. Functional coupling between CBF and cerebral metabolism may be disrupted [74, 307]; therefore, increased CBF in the setting of normal or decreased metabolism causes hyperaemia, or luxury perfusion, resulting in elevated ICP due to increased CBV [420].

ICP monitoring and Outcome

The causes and consequences of elevated ICP have a significant impact on outcome in TBI [6, 224, 279, 420]. ICP is elevated in 30-80% of head-injured patients without intracranial mass lesions [293, 325] and the majority of hospital deaths due to head injury are associated with elevated ICP [279]. Although there is no Class I evidence supporting the benefits of ICP monitoring and management, the supportive evidence is strong [40]. Currently ICP monitoring for patients with severe TBI and an abnormal CT head scan is recommended in adults and children based on the likelihood of elevated ICP [6, 40, 252].

However, questions about the benefits of ICP monitoring continue to circulate [12, 79, 81, 323]. Although the benefits of reducing ICP as an emergency appear to be clear when a patient has an intracranial mass lesion or is threatened by imminent herniation, ICP monitoring in the ICU is potentially limited in 2 important areas. First, elevated ICP may occur secondary to several different mechanisms, each of which may require a different optimal treatment. Second, all interventions for ICP have potential adverse effects, thereby possibly diminishing the benefit of measuring ICP. For example, the aggressive use of hyperventilation is no longer recommended because even though CO2 vasoreactivity is preserved in most patients after TBI, and hyperventilation is therefore effective in reducing ICP [265], the vasoconstrictive effects of hyperventilation may reduce CBF to ischaemic levels [246]. Therefore, in absence of identifying the cause of elevated ICP and monitoring for the effects of the intervention, ICP monitoring can be a blunt tool and may expose the patient to additional risks of ill-advised treatment.

However, the studies questioning the benefit of ICP monitoring all have methodological flaws [12, 63, 81, 323] that limit their arguments. Furthermore, uncontrolled elevated ICP poses considerable and well-characterised risks to the patient known to be associated with poor outcome, in particular cerebral herniation and ischaemia. Consistent with this, monitoring ICP and treatment of elevated ICP have been associated with better outcomes in several studies [40] and therefore ICP monitoring is still

recommended. Stronger evidence for the benefits or limitations of ICP monitoring may be forthcoming [63].

Indications for Monitoring and Thresholds for Treatment in Children

Indications for ICP monitoring in children vary between different institutions [50, 243]. In the United Kingdom, approximately 60% of children presenting with severe TBI undergo ICP monitoring but there is large between-centre variation [243]. Furthermore, and of greater concern, many patients receive ICP-targeted therapy without an ICP monitor *in situ* [243]. Yet, although there is this significant variability, it does appear that there is increasing conformance with published guidelines [87]. However, similar to the situation in adults, some question the benefit of ICP monitoring in paediatric TBI [275].

In children the definition of elevated ICP is less clear than in adults because of changing physiological norms with age. This is further complicated by the different pressure-volume index in children [325], uncertainty about what CPP targets are optimal [8], and whether the autoregulatory curve in children is similar to that of adults [380]. In adults, ICP > 20-25mmHg is considered abnormal and the threshold at which treatment should be initiated [41]. Lower thresholds for treatment are often considered for younger children, but there are no reliable data to support this. Currently, the recommended, and most commonly used, threshold for ICP treatment remains 20 mmHg [7, 243]. If the anatomical characteristics of the brain which determine the point at which a paediatric brain undergoes herniation is similar to that of an adult brain, and the autoregulatory curve is similar [380], then targeting a similar threshold makes sense, as long as an appropriate CPP is maintained. This threshold supported by the findings of Sharples et al [329] who found an inverse relationship between CBF and ICP > 20mmHg, and Shapiro and Marmarou [325] who found significant changes in the pressure-volume index when ICP was elevated above 20mmHg.

Methods of ICP Monitoring

Standard methods for ICP monitoring are used in children. Intraparenchymal devices are used most commonly. These include the Codman ICP Express (Codman, Raynham, MA) and the Camino device (Integra Neurosciences, Plainsboro, NJ). Complications are infrequent [166, 326]. Ventriculostomy is also used although less frequently [243], most likely because of difficulties in cannulating small ventricles in the typical child with diffuse swelling. However, where ventriculostomy is possible, the benefits of ICP reduction with CSF removal are appreciable. This may be of particular benefit in children because the pressure-volume index is such that small changes in volume result in significant changes in ICP [325].

Chapter 4

Cerebral Perfusion Pressure in Paediatric Severe TBI

A Debated Subject

The issue of what constitutes an optimal CPP target for both adults and children generates significant debate. Debate also continues about whether ICP-targeted treatment or CPP-targeted treatment is better. There is a well-known association between low CPP and poor outcome; however, this may largely reflect its association with elevated ICP. On the other hand, some argue that absolute ICP values are of lesser importance if adequate CPP can be preserved. Although several studies have shown the relationship between low CPP and poor outcome in TBI, whether this primarily reflects that association of both with increased severity of injury, or whether active modulation of CPP benefits patients, is much less certain. If the latter is true, the question remains: what is the optimal CPP for patients?

CPP-targeted Therapy

Higher CPP targets in adult TBI were recommended by Rosner et al [300, 301]. In theory, if autoregulation is intact, higher CPP will cause reduction of cerebral blood volume by the active vasoconstrictive response of cerebral arterioles. This may avoid the vasodilatory cascade associated with CPP levels at the border region of the lower breakpoint of autoregulation. In doing so, ICP would be actively managed and there would be less risk of low CPP-related ischaemic episodes. Elevated CPP may also improve CBF in ischaemic regions [76, 169, 331]. However, there are potential problems with this approach. First, autoregulation is commonly impaired after TBI; therefore, an increase in BP may have the opposite effect [34, 186]. Second, higher CPP may be complicated by increased microcirculatory dysfunction and exacerbate tissue oedema [102, 261]. Third, this CPP-targeted approach leads to a

significant increase in systemic adverse effects, most notably acute respiratory distress syndrome, without any clear evidence of benefit [294].

An opposite view emanated largely from Lund University in Sweden, where clinicians argued against targeting higher CPP, citing concern that this may exacerbate vasogenic oedema and elevated ICP. They proposed lower CPP thresholds (down to 50mmHg in adult TBI) using principles of brain volume regulation by aiming to limit oedema formation [22, 104, 129, 262]. Lower perfusion pressures are guided by microdialyis-based monitoring of metabolism [260, 261, 262]. Their outcome results have been as good as at any other centre and their argument is strengthened by the lack of metabolic perturbations seen at lower perfusion pressures in their reports. However, this approach has also not been without controversy [19]. Other studies suggest that CPP in the lower range may increase the incidence of ischaemic episodes [174] and that increased CPP improves brain oxygenation [76, 169]. Also, absolute CPP levels may not predict adequate tissue perfusion; therefore lower CPP levels may be hazardous in centres where measures of metabolism or tissue perfusion are not employed. To illustrate this point, Thees et al demonstrated in an experimental model of progressively decreasing CPP that electrical silence occurred over a narrow range of oxygenation but over a wide range of CPP [368].

A middle approach suggests that CPP should be individualised to the patient. However, the endpoint that should be targeted is not clear and there are several possibilities, all of which have potential limitations. These include optimal CPP based on maximal autoregulatory capacity, PbtO2, SJVO2, and microdialysis measures.

CPP in Children

In paediatric TBI, this already heated debate about CPP targets is further complicated by changing BP and ICP norms with age. Therefore, there is little agreement on what constitutes an appropriate CPP for age, or even the definition of hypotension. It is clear though that low initial BP correlates strongly with mortality (Chapter 2).

Several studies have examined various CPP thresholds in children with TBI, a summary of which reveals the uncertainty surrounding the subject. Jones et al considered a CPP threshold of 50 mmHg for children under 13 years old to be appropriate [170]. Chambers et al [56] used a novel pressure-time index to evaluate secondary insults in children, using critical CPP thresholds of 48, 54 and 58 for age-groups 2-6, 7-10 and 11-15 years respectively, and compared the duration of time below these thresholds with eventual outcome. The authors found the pressure-time index to have a high predictive value for outcome. In an earlier paper, the same group [58] used receiver-operating curves in the determination of outcome, finding 45 mmHg to be the minimum CPP threshold for outcome prediction in children. Prabhakaran et al [278] described 2 groups of children with severe TBI, one maintained at CPP > 50mmHg (ICP arm) and the other at CPP > 70mmHg (CPP arm); in this small study there appeared to be a trend towards better outcome in the CPP arm, but 2 patients in the CPP arm died while there were no deaths in the ICP arm. Vavilala et al [395] found that all children who had an admission systolic BP < 90 mmHg had a poor outcome, but that the 75th centile of systolic BP for age was a better predictor for outcome than the 90mmHg threshold. Downard et al [98] on the other hand found that CPP elevation > 50 mmHg was not associated with improved survival in their series of 188 patients, arguing that CPP management may simply be acting as a proxy for the avoidance of hypotension. Yet Hackbarth et al found that maintenance of an adequate CPP was the single most important factor for survival in paediatric TBI [134]. In their population, ≥ 80% survival could be expected if CPP was maintained > 50mmHg, and > 90% survival if CPP could be maintained > 60mmHg.

None of the above studies considered height for age in the estimation of MAP or CPP. As discussed above, height correlates better with skeletal age than with chronological age and is related to BP independently of age [299]. There are considerable differences in the BP normograms between children who are on the 3rd versus the 97th centile of height for age [136].

Current recommendations for paediatric TBI support the avoidance of CPP < 40mmHg in all children and targeting CPP > 50mmHg at the level of an option, while acknowledging that CPP management may require an age-related approach [8].

Chapter 5

Cerebral Haemodynamics, Autoregulation and TCD

Overview

This section concentrates on important clinical issues surrounding cerebral blood flow and cerebrovascular autoregulation in TBI, with an emphasis on the implications that these have for monitoring, especially TCD, and on general management and outcome in TBI.

1. Cerebral Blood Flow in TBI: Ischaemia and Hyperaemia

Cerebral Hyperaemia

Diffuse cerebral swelling is common in children with severe TBI. Hyperaemia, or vascular engorgement, was long thought by many to be the predominant cause of this swelling leading to elevated ICP in children with severe TBI. This was prominently argued by Bruce et al [43], who suggested that the predominant cause of diffuse swelling in children was hyperaemia and vascular congestion, based on measurements of CT head scan Hounsefield values and a subset of 6 children in whom CBF studies were done. More recently however, the role of hyperaemia as a cause of diffuse swelling has been questioned [245, 329, 420]. The diagnosis of hyperaemia is challenging [307] and even when it does occur, the relationship with elevated ICP is not obvious [245, 329]. When CBF values are compared with mean values for the age group the incidence of true hyperaemia appears to be much lower than previously believed [420]. Although there may not be an absolute statistically significant correlation between CBF and age, CBF values tend to increase from the lowest values at birth to a peak at age 3 to 5 years old and then decrease to adult levels [69, 420]. When compared to adult values,

CBF values in normal children are higher. Cerebral metabolic rate for oxygen and cerebral metabolic rate for glucose also appear to be low at birth and peak during early childhood but there are too few data to be more specific [380]. Therefore, when interpreting high CBF values in children with TBI, correct age-specific ranges should be taken into account.

Cerebral Ischaemia

In children with severe TBI as in adults, low CBF is associated with poor outcome [10, 329]. Low CBF is particularly common in the early phase after head injury [10, 36, 173, 392] and the cerebral metabolic rate of oxygen corresponds with these CBF levels [327]. Bouma et al demonstrated that more than 30% of patients have CBF levels below conventional ischaemic thresholds within the first 12 hours after injury, that low CBF correlated with poor outcome, and that BP augmentation improved these low CBF levels in some cases [35, 36]. When compared with normal CBF which is between 45-60ml/100g/min, critical values for cerebral ischaemia (from stroke models) occur when CBF drops to below 18ml/100g/min [23, 225, 333, 416] and this is associated with progressive electrical failure and EEG flattening. Mismatch between increasing glycolysis and limited oxidative phosphorylation produces cellular acidosis and net energy loss. Further reductions lead to membrane failure, and CBF < 10mls/100g/minute is thought to exist at the ischaemic core of an infarct [225]. The likelihood of developing irreversible tissue ischaemia is a function of both the depth and duration of tissue hypoxia [333, 416].

However, in TBI the relationship between CBF and metabolism is much more complex and low CBF does not necessarily equate with cerebral ischaemia because it may be appropriate for reduced metabolic demand or mitochondrial dysfunction. Also, 'normal' blood flow levels may be inappropriately low in areas with increased metabolism if there is uncoupling between CBF and metabolic needs. Therefore, metabolic needs after head injury, mitochondrial dysfunction, increased oxygen extraction and coupling between metabolism and CBF must be taken into account to correctly interpret absolute values of CBF, recognising that thresholds of CBF for irreversible injury in TBI differ

compared to those documented in stroke even though thresholds of cerebral metabolic rate for oxygen are similar [82].

The difficulty in diagnosing classic macrovascular ischaemia in patients with TBI, combined with the clear evidence of frequent ischaemia in post-mortem studies [128], may suggest that other mechanisms, such as diffusion limitation, may play a role in the development of tissue hypoxia in TBI [235]. The selection of patients for study, timing of the investigation, and method of measuring indices of ischaemia have constrained attempts to define the incidence of cerebral ischaemia after TBI. Therefore, the diagnosis of cerebral ischaemia or tissue hypoxia as a secondary event has remained elusive and the prevalence of ischaemia after TBI remains debated [35, 74, 75, 92, 343, 401].

2. Pressure Autoregulation

Normal Physiological Responses

Although there are several autoregulatory responses of importance in TBI, including the vascular responses to changes in PaCO2, metabolism, and PaO2, the phenomenon of pressure autoregulatory responses has attracted much attention recently. Since the earliest description of the response of cerebral vessels to changes in BP [118, 190], the phenomenon of pressure autoregulation (AR) in health and disease has been extensively studied. AR, or pressure reactivity, is a physiological response in which cerebral blood vessels vary in calibre inversely to changes in BP, thereby maintaining a (relatively) constant CBF. Therefore, cerebrovascular resistance varies with BP. Up to a MAP of 90 mmHg, changes occur in pial arterioles less than 200 microns in diameter, while between a MAP of 110-160mmHg, changes occur in vessels larger than 200 micron in diameter [181]. Pressure reactivity is generally active over a range of BP from MAP of 50-60mmHg to 150mmHg [272], and responds generally within seconds of the change in BP. In this active range, cerebral arterioles constrict as BP is elevated and dilate as BP is lowered. As BP is lowered cerebral blood volume increases as does ICP, depending on intracranial compliance [34]. Below and above the lower and

upper breakpoints respectively, CBF tends to vary linearly with changes in BP. Therefore, decreasing BP below the lower limit of AR decreases CBF and increasing above the upper breakpoint increases CBF and cerebral blood volume. These physiological responses have long been known to be active in normal brain [118], but more recently, the impairment of AR in TBI has been increasingly recognized.

Consequences of Impaired Autoregulation

When AR is impaired, blood vessel calibre varies passively with BP changes as does CBF. Therefore, if BP is elevated cerebral arterioles dilate and increase cerebral blood volume, which in turn increases ICP. Cerebral blood volume and ICP therefore, may vary passively with changes in BP [34]. However, when AR is intact the reverse occurs - decreased MAP may lead to increased ICP because cerebrovasodilation accompanies decreased CPP at the lower range of the autoregulatory curve. Kontos et al [181] demonstrated that the main effectors of cerebral blood volume changes in the area of the lower AR breakpoint are the small arterioles which can undergo diameter changes of 200%. These changes are sufficient to explain the ICP changes observed in response to changing BP [382]. Therefore, depending on the whether AR is intact or not, the same BP changes can have widely different cerebrovascular effects in individual patients.

Impaired AR also has implications for the adequacy of CBF to the tissues. At lower levels of CPP, impaired AR may limit the normal vasodilatory response to decreasing BP and exacerbate the adverse effect of hypotension on secondary ischaemia. Therefore, the status of AR has significant implications for the relationship between BP, cerebral blood flow, cerebral metabolism, cerebral blood volume and ICP. In summary, impaired AR increases the risk of cerebral ischaemia at lower CPP levels and cerebral congestion at higher CPP levels. These phenomena have important implications in TBI patients. The status of AR may 1) be associated with outcome, 2) impact choice of an optimal CPP, 3) increase secondary insults if impaired, 4) lead to unintended consequences with therapeutic interventions, and 5) allow manipulation of cerebral blood volume to treat raised ICP.

Complete or Partial Impairment of Autoregulation?

Many studies conclude that AR is preserved or lost in a binary fashion, but pressure reactivity may be partially disrupted and not completely lost [186]. This may result in a reduced vasoactive response to BP changes or a resetting of the limits of autoregulation, e.g. AR may be initiated at a higher CPP threshold. Several studies have tested the relative strength of AR as an index rather than as an absolute assessment (see below). Rosner et al [300, 301] suggested that the lower limit of AR is often shifted upwards after TBI; therefore, targeting higher CPP would avoid the vasodilatory cascade that results from CPP values at the lower range of the AR curve, where cerebrovascular dilation increases cerebral blood volume and therefore increases ICP (Chapter 4). Lang et al found that a lower breakpoint for AR occurred over a range of CPP values from 50mmHg to 85-90mmHg in adults[186]. However, ICP changes were used as surrogate markers of the status of AR, which may be misleading because ICP changes may also depend on the cerebral compliance at the time of testing and the agent used to induce hypertension. Furthermore, these are broad generalisations in a clinical situation where significant heterogeneity is encountered; therefore, they are not necessarily a guide to AR or optimal BP management in individual TBI patients.

Testing Autoregulation

a) Methods of Testing

The testing of the status of AR has been described using several methods, which include the use of Xe^{133} CBF studies [33, 247], TCD [346, 397], laser doppler flowmetry [184, 375], brain tissue oxygen [161], a pressure-reactivity index of the continuous relationship between MAP and ICP [346], and using arteriovenous difference in oxygen as a surrogate marker of changes in CBF [306]. The most commonly used bedside techniques involve passive observation of the spontaneous relationship between MAP and ICP over time and observation of CBF/FV responses to induced hypertension or hypotension [80, 83, 148, 149, 268, 345, 346, 356]. AR is often referred to as the static rate of AR to describe the response to a steady-state change in the BP (for example with a phenylephrine infusion) or dynamic AR to describe the response to a rapid change in BP (for example with the thigh cuff deflation test or carotid compression), both of which yield similar results although there may be occasional variations [145, 281, 369]. TCD evaluation of AR is widely used because it does not depend on the more cumbersome or invasive methods of determining CBF, it poses no radiation risks and it can be performed at the bedside [80, 195, 356, 397]. Determination of the static rate of AR by the TCD technique has been validated with PET and direct examination studies [254, 346].

An autoregulatory index (ARI) is used to describe the strength of the autoregulatory capacity. The equation used to calculate ARI is:

$$ARI = \%\Delta eCVR / \%\Delta MAP \text{ or } \%\Delta CPP$$ [268]

eCVR is the estimated cerebrovascular resistance and is the ratio of MAP/ FV. ΔeCVR and ΔCPP (ΔMAP) refer to the changes in the respective values during AR testing. ΔMAP is used when ICP is not being measured.

An ARI value of 1 implies that the strength of AR is maximal, a value of 0 implies complete absence of AR, and values between 0 and 1 reflect the relative strength of AR. Although the AR capacity is a continuum, an ARI of 0.4 is commonly used as a threshold to describe whether AR is intact or not [397], although others have used slightly higher values. Values for ARI < 0.4 are associated with impaired AR and values ≥ 0.4 are associated with intact AR.

b) Elevation of BP to Test AR

The magnitude of elevation of the MAP used to test AR is variable. Many studies elevate MAP to approximately 20% of its baseline value [33, 376, 397]. Others increase MAP over a larger range of 50-100mmHg [186]. The most information would be obtained from mapping the complete range of AR with lowering of the patient's BP to detect the lower range of AR and elevation of the BP to detect its upper limit. However, the latter approaches require substantially greater increases in MAP and may involve a higher risk to the patient. The former approaches may yield more limited information but may be more practical in the ICU. These provide practical information about the action of AR over a range of BP likely to be encountered for the individual patient, either spontaneously or as a consequence of intervention.

c) Agents Used to Elevate BP

The agents used to test static rate of AR are important because they may directly influence cerebrovascular dynamics and confound the examination of the effects of BP changes on FV. These include direct effects on vascular tone and an increase in the cerebral metabolic rate of oxygen by passage through the blood brain barrier. The effects of dopamine, adrenaline and noradrenaline have been examined in animals and humans in several studies that have produced conflicting data. In summary, the direct effects of these agents on CBF and ICP appear to be unpredictable and not necessarily limited to their effects on MAP [25, 103, 209, 248, 284, 285, 341, 348, 379]. Phenylephrine is the preferred agent to increase BP in the testing of AR [33, 141, 149, 186, 380]. Phenylephrine appears to have minimal direct effect on the cerebral vasculature as circulating phenylephrine does not reach concentrations shown necessary to effect degrees of vasoconstriction sufficient to influence cerebral blood volume significantly [181]; therefore, the direct effects of phenylephrine on CBF are thought to be negligible [62]. More recently the effects of arginine vasopressin on brain oxygenation and ICP have been tested against catecholamines [100] but less is known about its action in AR.

d) The AR-dependent Response of ICP to BP Changes

The ICP responses to a rise in BP during AR testing have been described as pressure passive, pressure active, and pressure stable [186]. Pressure passive responses are characterised by increased ICP with induced hypertension (impaired AR), pressure active responses by reduced ICP (intact AR), and pressure stable response by no changes in ICP. The pressure stable response is probably consistent with preserved AR, except perhaps in cases of very high intracranial compliance, which should be evident from the baseline ICP values. Lang et al [186] consistently demonstrated the change from a pressure passive to a pressure stable pattern at the lower limit of AR, which suggests that it usually represents active pressure reactivity. However, not all studies demonstrate a fall in ICP with increased BP [34]. The varying limit of the lower breakpoint of AR and the agents used for testing may explain these variable ICP responses to BP changes in patients who appear to have impaired AR [34, 247]. However, the relationship between impaired AR and elevated ICP is complex. Disturbed AR may aggravate intracranial hypertension, but intracranial hypertension may, in turn, impair AR [80, 85].

Can CPP be Optimised Based on the Autoregulation Profile?

Targeting an optimal CPP based on tested or observed AR responses is an attractive idea [347]. The optimal CPP is chosen based on the range of CPP over which AR is most active. Potentially this approach may achieve 2 goals: 1) it avoids the vasodilatory cascade associated with BP at the lower range of the AR threshold and achieves the lowest cerebral blood volume for a given BP, and 2) it should represent adequate perfusion on a global basis. This may be true when the lower breakpoint is known as it cannot be assumed that a universal threshold for CPP is optimal for all patients; therefore higher or lower CPP that is necessary for an individual patient may both have risks. A study by Kroppenstedt et al [182] would seem to support this concept. In their experimental model, both higher and lower CPP increased contusion volume, which was minimised over a relatively short range of CPP.

However, there are potential limitations of this approach. First, when AR is markedly impaired (ARI close to 0), decision-making about optimal CPP is challenging. Second, the CPP at which the AR response is maximal is not necessarily the CPP required to provide adequate perfusion. If compliance is adequate and ICP is not significantly raised, tolerating a lower CPP may be a safe option (and not associated with the risks of maintaining higher CPP). Third, it can be argued that the adequacy of perfusion can only be established by measures of substrate delivery or metabolism. Measures of the physical response of vessels cannot necessarily be equated with metabolism. Therefore, although this approach may be helpful to manage ICP, or avoid unwanted ICP spikes related to intact or impaired AR responses, the use of an optimal CPP based on pressure AR criteria alone may be limited if the adequacy of perfusion is not guaranteed.

The Frequency of Impaired Autoregulation in TBI

Impaired AR has been reported in one to two thirds of patients with severe TBI [34, 247, 265, 306, 327, 397] depending on the severity of the injury, the baseline BP (at the time of testing), the timing (length of time after TBI sustained) and the method of testing. In children, AR appears to be impaired in approximately 40% of patients at some point after sustaining TBI [380, 397]. The frequency of impaired AR varies with time after injury [83, 149, 376], and may differ between hemispheres in the same patient [315, 399]. Therefore, measurements at a single point in time may not reflect the true frequency of impaired AR in patients with TBI.

Impaired Autoregulation and Outcome in Adult and Paediatric TBI

Several studies have shown an association between impaired AR and poor outcome in adult and paediatric TBI [84, 144, 269, 345, 398]. Sharples et al [327] also showed that there was a relationship between CPP and cerebrovascular resistance in children with good outcome, but no relationship between these measures in children with poor outcome after TBI. Increased age and lower CPP appear to be associated with higher risk of impaired AR [144].

In comparison with the studies of AR in adults, there are much fewer studies in children with TBI [247, 327, 397]. Moreover, until recently these studies had not described the use of AR testing in the ICU environment where it may be used as a modality to guide treatment. Muizelaar et al [247] examined 26 children with severe TBI using repeated xenon[133] washouts. Sharples et al [327] described AR in 17 children using a modification of the Kety-Schmidt wash-in technique. Vavilala [397] et al examined 36 children with varying degrees of head injury severity while undergoing anaesthesia at a mean of 9.6 days after injury using TCD. These studies support the association of impaired AR and poor outcome in children with TBI.

However, whether the association of impaired AR and poor outcome reflects the relationship of both with increased severity of injury or whether impaired AR causes secondary insults, and therefore represents a therapeutically modifiable factor that influences outcome, is not clear. One retrospective study suggested that the status of AR may influence the choice of ICP- or CPP-directed treatment [155]. This subject is further explored in Chapter 19.

3. Transcranial Doppler

Introduction

The Doppler effect was named after Christian Doppler for the description of the change in frequency of a wave when the receiver and transmitter of a wave are moving relative to each other. In a pulsed Doppler instrument the probe is both the receiver and transmitter of the wave and moving blood reflects the wave back to the probe. TCD was first introduced by Aaslid in 1982 for insonation of the basal vessels of the circle of Willis using a 2 mHz Doppler probe [2]. Since then the instrument has become widely used for non-invasive estimation of intracranial hemodynamics. The utility of the instrument is based on the relatively constantly maintained diameter of the MCA under changing conditions of BP and PaCO2 [1]. Therefore, although absolute values may not correlate, changes in FV are proportional to changes in CBF in the insonated vessel. TCD FV correlates well with CBF as measured by PET, Xe^{133} and arteriovenous differences in oxygen [32, 256, 346, 366]. This relationship can be confounded by vasospasm, in which the diameter of the conductance vessel is altered; however, vasospasm can be detected by using the Lindegaard ratio [201].

TCD studies have been used for estimation of baseline cerebral blood FV, detection of cerebral vasospasm [59, 196, 228, 264], and in dynamic tests for determination of the cerebral vascular response to BP changes [195, 257], PaCO2 changes [255, 257], and metabolic suppression [195, 255]. Use of TCD has also been reported for the noninvasive estimation of ICP and CPP [29, 314], and in the diagnosis of brain death [240].

Insonating the MCA in Adults and in Children

The MCA is the most commonly insonated intracranial vessel and a transtemporal approach is generally used. The proximal portion of the MCA is identified at a depth of 50-55 cm from the surface in adults. This distance is usually shorter in children, depending on age. Optimal depth of insonation

also depends on other physical factors, such as scalp swelling after trauma. The depth which gives the highest velocity is usually chosen for measurement. In general, TCD velocities are a reliable estimate of true velocities in the vessel. For angles of 0-30% between the ultrasonic beam and the intracranial artery the maximum error should be less than 15% [2]. Practical difficulties with maintaining long term insonation of the MCA limit the use of TCD as a continuous monitoring tool in TBI.

TCD FV_{MCA} parallels the changes in CBF with age. In newborns, FV_{MCA} is approximately 24 cm/s. This increases with age to peak at 97 cm/s at 6 to 9 years old, and thereafter decreases to adult values of approximately 50 cm/s [380]. The peak mean FV_{MCA} as reported in TCD studies occurs at a slightly higher age than reports of peak CBF for age (see above). There also appear to be slight gender differences in anterior and posterior circulation FV [396].

Pulsatility Index

Under constant conditions of BP and PaCO2, the pulsatility of blood flow through the conductance vessel reflects distal cerebrovascular resistance. A pulsatility index can be calculated which reflects this. The most commonly used index is the Gosling index [126]:

$PI = (FV_s - FV_d) / FV_{mean}$, where FV_s is Systolic FV, FV_d is diastolic FV and FV_{mean} is the mean FV.

Several studies have suggested that the PI is useful for the non-invasive estimation of ICP and CPP in TBI [29, 60, 200, 242, 283, 344, 404] and of ICP in hydrocephalus [249, 277, 310]. In particular, Bellner et al found a strong correlation between PI and ICP in adult TBI ($p<0.0001$, correlation coefficient 0.938) and that ICP > 20mmHg can be detected with a sensitivity of 0.89 and specificity of 0.92 [29]. Homburg et al found a 2.4% increase in PI per mmHg increase in ICP [154]. However, very few data exist on the PI in children with TBI. Meyer et al [238] reported improvement of PI after evacuation of acute subdural haematoma in infants and Trabold et al [378] reported that increased PI was independently associated with poor outcome. This topic is further explored in Chapter 18.

Vasospasm

Vasospasm can be diagnosed using the Lindegaard index which was described in a study that compared TCD recordings and angiographic findings [201]:

Lindgaard index = FV_{MCA} / FV_{ICA}, where FV_{MCA} is the FV in the MCA and FV_{ICA} is the FV in the ICA

The relevance of this ratio is based on the fact that, unlike the intracranial vessels, the extracranial ICA is not involved by vasospasm; therefore velocity changes in this vessel reflect changes in CBF whereas changes in intracranial vessel FV may arise from increased CBF or narrowed arterial diameter, as in vasospasm. When vasospasm occurs the ratio increases, and vasospasm is likely if the mean FV_{MCA} is >120 cm/s and the FV_{MCA} / FV_{ICA} ratio is >3 [201]. Mild vasospasm has been defined as Lindegaard ratios between 3 and 4, moderate between 4 and 6, and severe >6 [264]. Vasospasm confounds the relationships between TCD FV and metabolism and between ICP and PI. In adult TBI, vasospasm may be common, particularly in the late phase [227, 228, 264, 419]; however, vasospasm seems to be rare after paediatric TBI [213].

Chapter 6

Brain Oxygenation Monitoring: An Overview of Methods with a Focus on Brain Tissue Oxygen Tension Monitoring

Introduction

A key strategy in the management of patients with severe TBI in the ICU is to provide adequate oxygenation to the brain to avoid secondary injury. Therefore, much attention has been focused on methods for examining and monitoring oxygenation of the brain after TBI. Several methods have been used that are worth discussion. Widespread adoption of any single method has been restricted by limitations inherent in all of these forms of monitoring. Commonly used methods for direct and indirect (CBF as a surrogate marker and microdialysis for metabolism) monitoring of the adequacy of brain oxygenation are reviewed briefly below. PbtO2 monitoring is reviewed here in greater detail because of its use in the cohort of patients that form the bulk of this thesis. Continuous EEG monitoring may also be used for the detection of subclinical seizures and assessment of level of consciousness [407] in the ICU, and may also demonstrate changes secondary to brain ischaemia, but is not reviewed here.

Positron Emission Tomography

The gold standard for examining oxygen and metabolic indices in the brain is PET scanning. However, very few centres have access to PET and additional infrastructure is required to generate unstable isotopes of oxygen for complete investigation. Also, PET scanning generally requires patients to be stable and it is temporally restricted in that it provides only a snapshot of oxygen metabolism at one point in time. TBI is a dynamic condition and ischaemic episodes of short duration may have profound significance on outcome. For these reasons PET plays little role in the continuous

management of patients. However, PET has a major role to play as a research tool for validation of other brain oxygenation techniques and determination of metabolic and physiologic responses to intervention [75, 91, 132, 158, 263, 401].

Microdialysis

Microdialysis involves the parenchymal insertion of a microcatheter perfused with a physiological solution at ultra-low flow rates. This allows free diffusion of water and solutes from the surrounding interstitial fluid to the perfusing solution. Tissue concentration gradients determine diffusion across the semi-permeable membrane, which allows samples to be collected and analysed. Important markers of brain metabolism can thus be analysed, including lactate, pyruvate (lactate/pyruvate ratio), glucose, and glutamate [28]. Depending on the pathology, the catheter can be placed in normal-appearing brain or in a peri-contusional location. Most microdialysis work has been done in adults; there are very few studies of microdialysis in children [292, 372, 374].

One of the major limitations to the widespread use of microdialysis as a clinical tool in the ICU is the infrastructure and expense required for semi-continuous monitoring. A pump is required to infuse the catheter with dialysate, vials have to be changed on a regular basis and an analyser for the samples is required. Therefore, there are substantial nursing or technician requirements for the system to work optimally. Furthermore, current technology does not support continuous monitoring; therefore ischaemic episodes may be missed or intervention may be delayed. Also, there is some concern that microdialysis measures detect ischaemia at critical thresholds of CBF reductions below 20mL/100g/min, but may not provide an 'early warning system' at levels of oligemia that imply impending ischaemia [312]. Lactate typically rises when PbtO2 is less than 10mmHg in experimental and human studies [146, 312] and glutamate only rises at very low levels of PbtO2 [146]. These concerns have limited the widespread use of microdialyis in the ICU; however, it remains an invaluable research tool, particularly for the determination of the tissue response to therapeutic intervention.

Jugular Bulb Venous Saturation

The use of SJVO2 monitoring is common in the management of TBI patients, if not widespread. Most of the work that has been published on SJVO2 has been in adult TBI. Very little is known about SJVO2 in paediatric TBI. The procedure for placement of the catheter is generally straightforward. The tip of the catheter is optimally placed above the level of C1/C2 disc to minimise contamination from the facial vein. Correct placement of the tip of the catheter is important because the utility of SJVO2 is based on the fact that the bulb of the internal jugular vein drains mostly intracerebral blood. Incorrect placement, or shift of the catheter tip, may contaminate samples with blood from the external carotid system. There is debate about which side should be monitored. Some choose the side of worst pathology, or bilateral placement, however, most commonly the side of dominant venous drainage is preferred (assessed by compression of each internal jugular vein and separately observing the rise in ICP).

SJVO2 may be useful as a global measure of cerebral oxygenation. Interpretation of SJVO2 is based on the balance between supply (cerebral oxygen delivery) and demand (cerebral metabolic rate of oxygen). The arteriovenous difference of oxygen and the cerebral extraction of oxygen can also be calculated. Monitoring can be performed intermittently (intermittent samples drawn) or continuously (with a fiberoptic catheter). Management of SJVO2 in the ICU is directed at maintaining levels > 50%, although there is some debate on what threshold for treatment is optimal and whether normal values may be even lower than previously believed [67]. High and low levels of SJVO2 have been associated with poor outcome [77, 210]. SJVO2 has been compared to PbtO2 monitoring in several studies that demonstrate good correlation between the 2 methods in some but not all patients [125, 131, 175, 391]. High SJVO2 readings may occur despite low PbtO2 in patients with focal ischaemia and even in patients near to brain death due to shunting [391]. The main limitations of SJVO2 relate to the failure to detect regional ischaemia [74, 131] and the technical difficulties that reduce the time of good quality monitoring [88].

Because SJVO2 is a measure of global oxygenation, regional ischaemia may occur without reduction in SJVO2 levels. Coles et al [74] demonstrated that, on average, approximately 170mls (or 13 ± 5%) of brain was ischaemic before SJVO2 dropped below the threshold of 50%. This limitation may be of greater significance in patients with focal injury. Technical problems may reduce the amount of time that the catheter produces useful data (time of good quality data). Positional changes of the head, microthrombi at the tip of the catheter, and the need for repeat calibration significantly reduce the amount of time of good quality data. In centres that focus on SJVO2 it appears that this time of good quality data is high [125]; however, in average centres this figure may decrease to less than 50% [175]. Latronico et al [191] found that data from SJVO2 only marginally influenced management, that only 3.4% of observations were below the threshold for treatment and that there was substantial difference between the 2 sides. However, these issues are debated [355].

CBF Monitoring

A number of methods have been described to monitor CBF (global or regional) or flow velocity as a surrogate of CBF, including Xe^{133} perfusion scans, xenon-enhanced CT scans, single photon emission CT, PET, the Kety-Schmidt technique, the thermodilution method, laser doppler flowmetry, perfusion-weighted MRI, and TCD (flow velocity as a surrogate marker). Some techniques are cumbersome and cannot be used for continuous monitoring. Others may be more practical for the ICU but measure surrogate markers of CBF (such as TCD). More recently, continuous local CBF monitoring in the ICU has become available [383]. Although a significant advance, it is limited, similar to PbtO2 and microdialysis monitors, in that it monitors a focal region of brain. However, it may yield important complementary information similar to the above-mentioned modalities.

A major limitation of CBF monitoring is the uncertainty of the relationship between CBF and metabolism in TBI patients. Although flow and metabolism are tightly linked in healthy individuals, after TBI this relationship may be disturbed. Therefore, absolute levels of CBF may not be reliable.

High CBF may be associated with increased metabolism or may be inappropriately high, as in hyperaemia. Low CBF may occur secondary to depressed metabolism or may reflect true ischaemia.

Near-infrared Spectroscopy

NIRS is a non-invasive optical technique that uses the principles of infrared light transmission and absorption to reflect the concentrations of haemoglobin and deoxyhaemoglobin to measure oxygenation in tissues about 2 cm below the surface. Different methods include time-resolved, spatially-resolved and phase-resolved spectroscopy [16]. Transillumination is more difficult in adults and older children than in neonates, for whom NIRS is more established. While there are many reports of the usefulness of NIRS when there is no brain injury, as in cardiac anaesthesia [250] and carotid endarterectomy [15], similar reports in TBI are limited. Of those that are published, some demonstrate promising results [11, 153] but others raise concerns that the correlation with SJVO2 and PbtO2 is poor [46, 251]. Technical factors that may interfere with signal reliability (either no signal or an unreliable one) include a wet chamber between the optode and skin, subdural air after craniotomy, extracranial contamination, scalp swelling, subdural blood, subarachnoid haemorrhage, and brain swelling. Normal NIRS values have been found with complete ischaemia [319]. Therefore, the use of NIRS in TBI may be limited with current technology [394, 408]. However, the development of newer technologies may alter this [121].

PbtO2 Monitoring

Background

Local brain tissue oxygen tension can be monitored with a catheter inserted into the parenchyma of the brain, usually into white matter. Two systems have been commercially produced, namely Licox (Integra Neurosciences, Plainsboro, NJ) and Neurotrend (Codman, Raynham, MA). The latter also measured tissue pH, temperature and PCO2 but is no longer available. The Licox monitor is a Clarke-

type electrode that contains 2 electrodes covered by a membrane. The amount of O2 diffusing across this membrane depends on local tissue pO2 and determines the voltage signal between the 2 electrodes [332]. Initial animal work and bench tests, followed by human studies, confirmed the reliability of the PbtO2 signal, *in vitro* accuracy, and the low sensitivity drift and zero drift over time [90, 150, 175, 207, 233, 415]. The sampling area is approximately 14-17mm^3 [175, 188]. Local tissue damage from the catheter is minimal [415] and complications are rare [90]. The time of good quality data is in the region of 99% [90] and repeat calibration is not required. Although the PbtO2 readings are usually stable within 1 hour of insertion, sometimes the adaptation period may take up to 2 hours [90, 312, 388].

Normal and Abnormal PbtO2 Values

Normal values in humans are not precisely known. Because the PbtO2 value is influenced strongly by local CBF, the value varies widely depending on the metabolic activity and diffusion characteristics of the region being monitored. However, variability may be reduced during periods of ischaemia [312]. Extrapolation from studies which have measured PbtO2 in animal work and human studies monitoring relatively normal brain suggest that normal values for PbtO2 are around 25-30mmHg [89, 175, 188, 207]. An increased likelihood of poor outcome is noted as PbtO2 falls progressively below 20mmHg [384]. Scheufler et al [312] demonstrated in an animal model that CBF levels below 20ml/100g/min correlated with PbtO2 levels below 10mmHg. This 10mmHg threshold also correlates with critical thresholds related to outcome in human studies [175, 384]. PbtO2 < 10mmHg is associated with perturbations in microdialyis parameters, decreased mitochondrial function and impaired neuronal activity [146, 156, 312]. Studies of PbtO2 in aneurysm surgery best demonstrate the decline in PbtO2 associated with ischaemia due to temporary clipping [95, 151, 174].

PbtO2 values also require interpretation based on the location of the probe. The PbtO2 monitor may be placed in normal-appearing white matter or close to radiographically-identified injured or 'lesioned' brain [311]. PbtO2 in normal-appearing brain appears to reflect changes in global perfusion [168, 175, 302, 303, 312, 388], although not all investigators agree on this [160], Pericontusional brain may demonstrate altered

pathophysiological characteristics that require a different interpretation compared to 'non-lesioned' brain [131, 168].

Factors that Influence PbtO2

The best descriptor of what PbtO2 monitoring in the brain reflects is debated. Often considered a measure of the balance between supply and demand of oxygen in the tissues, it is also influenced by other factors. PbtO2 has variably been associated with CBF [96, 97, 164, 385], product of blood flow and oxygen content [415], mean transit time of blood through the brain [142], arteriovenous difference of oxygen [296] and end-capillary venous PO2 [132, 312]. Some of the important practical factors that influence the PbtO2 value are discussed below.

a) PbtO2 and PaO2

Being a measure of the partial pressure of oxygen, PbtO2 is significantly affected by PaO2. Therefore, even in conditions where arterial blood is near full saturation and increased PaO2 contributes little to improved arterial oxygen content, increased PaO2 is followed by increased PbtO2 [236]. Accordingly, the arteriovenous difference of oxygen strongly influences PbtO2 [296]. Similarly, progressive systemic hypoxia leads to a decline in PbtO2 and increased anerobic metabolism [72, 197, 415]. A potential limitation of this is that the ventilator FiO2 setting may significantly influence the PbtO2 reading in absence of substantial changes in oxygen delivery. However, dissolved oxygen may be preferentially used for tissue oxygenation [133, 358] and the partial pressure of oxygen in the tissues may be important in overcoming tissue barriers to diffusion (see below). The relative benefits of hyperoxia on PbtO2 and metabolism in TBI though, are currently debated [91, 211, 263, 373]. This topic is further explored in Chapter 17.

b) PbtO2 and PaCO2

PbtO2 varies with changes in PaCO2 if cerebrovascular CO2 reactivity is preserved [131, 160, 214, 316]. Under controlled conditions, these changes are linear [141]. The PbtO2 changes occur largely secondary to the vasoactive effects of PaCO2 changes. Therefore, hypocarbia may induce or worsen cerebral ischaemia and relative hypercarbia may improve local cerebral blood flow and therefore improve local oxygenation in areas at risk of ischaemia [214]. However, if hypercarbia significantly increases cerebral blood volume, and therefore ICP, the reduced CPP may have less predictable effects on PbtO2. This, and variations in the strength of CO2 reactivity in the cerebral vessels as well as different responses in abnormal tissue, may account for occasional 'paradox' reactions of PbtO2 in response to CO2 changes [89, 131]. Although moderate-severe hyperventilation without monitoring brain oxygenation is no longer recommended [5, 246], there continues to be debate regarding the extent of the risk of secondary ischaemia due to hyperventilation in human TBI [73, 92, 93].

c) PbtO2 and ICP

Elevated ICP may reduce PbtO2, either by the local tissue pressure effect or by reduction of CPP. Reports of decompressive craniectomy and barbiturate therapy in adult TBI have demonstrated improved PbtO2 after relief of ICP [163, 349]. However, when results are pooled an overall relationship between ICP and PbtO2 may not be demonstrable [388] because of the many other factors that influence PbtO2. This topic is explored further in Chapters 11, 13 and 15.

d) PbtO2 and CPP

Several studies have examined the relationship between PbtO2 and CPP but have produced conflicting results [14, 45, 76, 89, 169, 219, 289, 353, 381]. Most studies examining the effects of induced hypertension on PbtO2 have demonstrated an increase in PbtO2 in response to augmented CPP; however, this has not been a universal finding. To some extent these results may reflect variations in the strength of AR and the varying relationship between CBF and CPP. In experimental models,

PbtO2 shows a close relationship with changes in CBF [141, 415]. Therefore, PbtO2 may have a close relationship with progressive oligemia and warn of impending ischaemia. In the study by Scheufler et al [312], a progressive decrease in CPP was followed by decreasing CBF and increasing oxygen extraction fraction, while cytochrome oxidase redox level and PbtO2 showed parallel and progressive decreases.

e) PbtO2 and Hb

Isovolemic haemodilution reduces brain oxygenation and increases lesion size in TBI under experimental conditions [137], and PbtO2 decreases after haemorrhagic shock but responds to resuscitation [178, 215, 216]. Results of studies such as this, combined with knowledge of the important role that Hb concentration plays as a carrier of oxygen and in determining oxygen content of blood, suggest that the avoidance of significant anaemia in TBI is warranted. However, the optimal thresholds for transfusion are unclear because transfusion has potential systemic adverse effects, transfused stored blood does not have the same oxygen carrying capacity as the patient's blood, and the impact of the change in rheology in the microvasculature is uncertain. Two centres have examined the effect of blood transfusion on PbtO2 in adult TBI [193, 194, 338]. Blood transfusion had a variable influence on PbtO2 and the magnitude of change in PbtO2 was not readily predicted by pre-transfusion characteristics. Several potential factors may influence the effect of Hb and blood transfusion on PbtO2, including the underlying haemodynamics of the patient, baseline brain oxygenation, baseline Hb, age of the stored blood and alterations in rheology. The impact of blood transfusion on PbtO2 in paediatric TBI is examined in Chapter 16.

f) Diffusion Barriers to PbtO2

O2 transport in the tissues occurs by diffusion, which is affected by PaO2 [27]. PO2 decreases nonlinearly in the extracellular space with increasing distance from the vessel [313] and so the diffusion distance between the capillary and the cell is an important factor determining intracellular O2 tension. In TBI microvascular factors that may increase the diffusion distance for O2 include cytotoxic cell

swelling, perivascular edema, collapsed capillaries and arteriovenous shunting [235]. Therefore, diffusion-limited tissue oxygenation in TBI may be as important as perfusion-limited ischaemia, but more difficult to diagnose. If these factors play a significant role in impairing O2 diffusion to the cell, the partial pressure of O2 in the capillary may be of greater significance than in normal physiology.

PbtO2 and Outcome

Since the early studies of PbtO2 in TBI in the Netherlands and Germany in the early 90s [207, 233], several studies have examined the relationship between PbtO2 and outcome after TBI in adult patients [26, 350, 351, 384, 388, 391, 417]. Low PbtO2 occurs most commonly in the first 24 hours after TBI [388, 391], which is consistent with lower CBF, increased lactate and cellular acidosis seen in this time period [36, 70]. The risk of poor outcome after TBI has been linked to the depth and duration of low PbtO2 [384, 388]. For example, Valadka et al [384] demonstrated that the longer PbtO2 values were below 20 mmHg, the greater was the likelihood of dying, with the difference between patients alive and dead becoming significant at PbtO2 values less than 6 mmHg (the difference gradually widening the lower the threshold became). PbtO2 deteriorates to zero when brain death occurs [267, 339]. Two studies have examined intervention in PbtO2-monitored patients with historical controls and have suggested that a PbtO2-targeted approach may benefit patients [234, 350]. Meixensberger et al [234] compared 2 groups of patients, both of which had PbtO2 monitors inserted; however, PbtO2 was treated only in the second group, using CPP augmentation when PbtO2 was reduced. The PbtO2-treated group demonstrated a lower frequency of tissue hypoxic episodes and a greater likelihood of favorable outcome. Stiefel et al [350] found that patients treated with a PbtO2 monitor had a significantly lower mortality compared with patients in a historical cohort at their institution who were treated with only ICP monitoring. No randomised trials have been performed to date.

Only 2 reports have been published on PbtO2 in children, both of which involved relatively small numbers. Narotam et al [253] evaluated 16 patients who had a relatively high mean age of 14.65 years. In their series there were 6 deaths (37.5%); no patients with normal initial PbtO2 died. Stiefel et al [352]

reported 6 children with severe TBI, in whom PbtO2 was significantly lower if ICP was higher than 20 mmHg and CPP lower than 40 mmHg.

Section B

Chapter 7

Introduction to Patient Studies

Section B focuses on discrete studies which have been structured around specific questions from the observational data collected from children who were treated for severe TBI.

Guide to the Chapters

Chapter 8 summarises the process of data collection for these studies and the categories of data extracted. *Chapter 9* discusses the broad principles of the ways in which these children were managed, including what thresholds for treatment were used and what interventions were employed. *Chapter 10* summarises the clinical and demographic, physiological and treatment variables in a cohort of 52 children which form the core of this analysis and on which the subsequent chapters are largely based. The data are analysed to detect the frequency of derangements of all physiological variables. The subsequent chapters are largely based on this cohort (with exceptions as noted) and pose the following questions:

Chapter 11: 1) what is the association between PbtO2 and other variables, and 2) what are the associations between clinical and physiological variables, particularly PbtO2, and outcome?

Chapter 12: what is the association between monitored variables and the risk of developing delayed cerebral infarction?

Chapter 13: does adherence to treatment targets avoid brain hypoxia?

Chapter 14: what is the effect of ICP reduction with DCH on PbtO2?

Chapter 15: what effect does blood transfusion have on PbtO2 in children?

Chapter 16: does the use of prognostic grading scores predict the risk of secondary insults?

Chapter 17: what effect does normobaric hyperoxia have an PbtO2 in children with TBI?

Chapter 18: what are the relationships between TCD-derived variables and ICP, CPP and PbtO2?

Chapter 19: what is the relationship between the status of autoregulation and clinical factors, including the ICP and PbtO2 responses to changes in BP?

Chapter 8

Methods of Data Collection in the Patient Studies

Introduction

This section summarises the process of collection, management and interpretation of data for the subsequent chapters. Three broad categories of data were collected: 1) clinical and demographic, 2) physiologic, and 3) outcome data. Various treatment factors were also collected to supplement the analysis. The chapter ends with a discussion of the broad statistical approaches to the collected data.

Admission Clinical and Demographic Data

General demographic and clinical data collected on admission included: age of the patient, weight and height, gender, mechanism of injury, time of injury, other injuries sustained, initial Hb, and initial MAP.

The following time sequences were calculated: time of admission (after injury), time of monitor insertion (time from injury to monitor insertion), duration of monitoring, and length of ICU stay.

Pre-hospital potential episodes of hypoxia and hypotension were recorded using standard definitions. Hypoxia was defined as SaO2 <90% (SaO2<90) and hypotension was defined as systolic BP < 90mmHg (SBP<90) for consistency and comparison with other studies. However, initial MAP was also used and analysed in conjunction with these.

In addition the following classifications and grading systems were recorded:

Glasgow Coma Scale (GCS): Postresuscitation GCS was recorded in all patients. The Pediatric Coma Scale was used for preverbal children [335, 336]. The motor component of the GCS was separately documented.

Paediatric Trauma Score (PTS): The PTS includes 6 variables: weight, SBP, mental status, airway maintenance, skeletal injury and open wounds [364, 365].

Paediatric Index of Mortality (PIM2): The PIM 2 [337] is a specialised paediatric score that uses the following variables collected on admission to the ICU: 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.

Pupil reactivity (pupils): In this study, postresuscitation pupillary reactions were classified as bilaterally reactive (1), unilaterally nonreactive (2), or bilaterally nonreactive (3). The influence of medications was excluded.

Head CT classification: The severity of TBI was classified according to the Marshall system [223] based on admission head CT scan findings. These categories are as described in Chapter 2.

Patient Age: Age was used in this study to classify patient risk and to control for possible associations between variables since age may influence outcome [99, 244] and physiological thresholds [56].

Physiological data

Physiological variables: Intracranial monitoring was started as soon as possible after admission to the ICU and was continued until both ICP and PbtO2 were controlled for > 48 hours or the patient died. ICP, CPP, PbtO2 and FiO2 were recorded hourly. Data for some patients were also recorded in 10-second samples using the ICMPlus® software recording system (University of Cambridge, U.K.);

however, for consistency across all patients only manual recordings were used for analysis. Arterial blood gas samples were taken routinely as per normal ICU protocols and when clinically indicated. Recordings during suctioning and various tests (e.g. during hyperoxia and AR tests) were identified and excluded from general analysis. PbtO2 data were collected for analysis after allowing for a 2-hour run-in period to avoid analysis using potential artefactual data from a stabilising catheter. Recorded data were checked for errors in transcription using a 3-step process. All data were managed in Microsoft Excel and Access databases (Microsoft Corp., Redmond, WA). Raw observations were used whenever possible; however, for more detailed analysis, the following values were also calculated:

PbtO2: When patients had 2 PbtO2 monitors *in situ*, the lower reading of the 2 catheters was used to calculate the incidence of low PbtO2. PbtO2 values were calculated for each patient as: lowest PbtO2 recorded during the monitored period ($PbtO2_{low}$), mean PbtO2 during the first 24 hours of monitoring ($mPbtO2_{24}$) and the number of episodes of PbtO2 < 10mmHg (PbtO2<10) or PbtO2 < 5mmHg (PbtO2<5) experienced. In addition, to complement these data, and because the likelihood of irreversible brain injury is determined by both the depth and duration of hypoxia, a measure of low PbtO2 that reflects both was sought. Therefore, for each episode of PbtO2 < 10mmHg (PbtO2='X'mmHg) in each patient, the value 10 minus XmmHg was calculated (10-X). If PbtO2=10mmHg represents a critical tissue hypoxia threshold[188, 312, 384], then (10-X) represents the depth of hypoxia. Thereafter, all of these (10-X) values were averaged for each patient (depth of hypoxic insult). This average was then multiplied by the number of episodes that PbtO2 was less than 10mmHg in that patient (duration of insult). This was termed the Time-Hypoxia product to reflect the overall tissue hypoxia burden.

ICP: The following ICP values were recorded for each patient: mean ICP for the duration of monitoring (mICP), mean ICP for the first 24 hours of monitoring ($mICP_{24}$), the number of episodes of that ICP was > 20mmHg (ICP>20), the mean of all episodes when ICP was > 20mmHg (mICP>20), and the highest ICP (ICP_{peak}) experienced.

CPP: Potential CPP insults were calculated for each patient as: initial CPP ($CPP_{initial}$), the lowest CPP experienced (CPP_{low}) and the number of episodes that CPP was < 40mmHg (CPP<40) and < 50mmHg (CPP<50).

Oxygenation and Ventilation: Systemic hypoxia was defined as PaO2 < 60mmHg (PaO2< 60) on arterial blood gas (ABG), or SaO2<90% on peripheral oximetry or ABG. The lowest PaO2 ($PaO2_{low}$) observed during ICU stay was also recorded. PaCO2 was recorded as end-tidal CO2 in some patients. For consistency, only arterial samples of PaCO2 were used. Both PaO2 and PaCO2 were recorded in kPa. For associations between PaO2 and PbtO2, both are expressed in mmHg for ease of use (Chapter 17).

Haemoglobin: Arterial Hb was recorded as initial Hb ($Hb_{initial}$), lowest Hb (Hb_{low}) and mean Hb for the duration of the ICU stay (mHb).

Serum Sodium: The concentration of serum sodium was recorded in mmol/L.

FiO2: The ventilator inspired fraction of oxygen (FiO2) was recorded as an hourly variable.

Other monitored and calculated parameters: Other parameters that were also recrded or calculated were the TCD variables, autoregulation indices, and PbtO2/PaO2 ratios related to the FiO2 testing of the PbtO2 catheters. Further details of these parameters are given in the sections on TCD, autoregulation and hyperoxia respectively (Chapters 17 to 19).

Treatment Factors

Specific treatments that patients received were recorded. These included the use of thiopentone, DCH, RBCT, and inotrope support.

Clinical Outcome Evaluation

Patients were evaluated at follow-up clinical examinations. Assessments by the neurosurgeon, rehabilitation therapists (speech and language, occupational and physical therapists), developmental paediatricians and school reports (where appropriate) were considered in final outcome evaluation. Outcome was recorded using the GOS [165] dichotomised into favourable (GOS 4, moderate disability or 5, good recovery) and unfavourable (GOS 1-3, death, persistent vegetative state and severe disability) outcome. Although the GOS was not specifically designed to examine paediatric outcome it is a commonly used scale for assessment of paediatric head injury and most neurosurgeons are familiar with its use [54, 66, 99, 172, 176, 229, 395]. However, the Paediatric Cerebral Performance Category Scale (PCPCS) was also used to confirm these data [114, 115, 159]. The PCPCS was also dichotomised (1-3 for favourable outcome and 4-6 for unfavourable outcome). Deaths were recorded as having occurred in the ICU (ICU mortality), in the ward (ward deaths), within 30 days (30d mortality), and all (total mortality).

Statistical Analysis

All data were analysed with R statistical computing (http://www.r-project.org) and Stata software (version 7.0, College Station, TX) by a statistician employed at the University of Cape Town. In general data were examined with combinations of correlation (Spearman's and Pearson's, coefficients reported as r), univariate analysis and multivariate linear regression or logistic regression analysis where appropriate. Where necessary, additional statistical tools were used, including linear mixed effects regression models, proportional odds regression models and general estimating equations. Significance was set at p=0.05. P-values are two-tailed. Descriptive statistics are reported as mean ± SD or median and interquartile range (IQR) and range, depending on distribution characteristics. In general, variables with relatively normal distributions are described as mean ± SD, while those with skewed distributions are described as median (IQR). Specifics of the statistical analysis for each study are reported individually in the corresponding section. Wherever possible, raw data (original observations) were used rather than summary data.

Chapter 9

Selection of Patients and General Management Protocol

Selection of Patients

Data were collected prospectively from a consecutive series of paediatric patients who underwent PbtO2 and ICP monitoring for severe TBI (GCS ≤ 8) at Red Cross War Memorial Children's Hospital between June 2006 and May 2008, which forms the bulk of the analyses in this thesis, although some chapters report patients over a shorter period of time corresponding to when the analysis was done. Where the latter is the case, the corresponding dates are specified. All patients less than 15 years old, which is in accordance with the admissions policy of the hospital.

Children with TBI were considered for monitoring if their postresuscitation GCS was ≤ 8 or deteriorated to this level after admission, unless early extubation was contemplated for a rapidly waking patient, brain death was diagnosed or the patient was considered to be unsalvageable on initial assessment (GCS 3/15, dark brain on admission head CT scan and fixed dilated pupils). Occasional patients did not receive monitoring because PbtO2 catheters were not available or all Licox machines were in use. All of these patients survived. Outcome analysis is restricted to the patients who received PbtO2 monitoring.

Patients were resuscitated according to the Paediatric Advanced Trauma Life Support guidelines, underwent endotracheal intubation and head CT scanning and were mechanically ventilated in the paediatric ICU. Informed consent was taken from the parents of the child for intracranial monitoring.

Management of Patients

General

Management of ICP and CPP were broadly in keeping with the Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents [4]. Significant intracranial haematomas were surgically evacuated. General ICU treatment was directed towards avoiding systemic hypoxia and hypotension, and actively managing ICP, CPP, and PbtO2. Basic management consisted of analgesia (morphine), sedation (midazolam and/or diazepam), elevation of the head of the bed to 15 to 20°, maintenance of rectal temperature between 36 and 37°Celsius, and maintenance of serum sodium ≥ 140 mmol/L.

ICP management

ICP was measured with a ventriculostomy device or an intraparenchymal monitor. Two commercially available parenchymal monitors were used: Codman ICP Express (Codman, Raynham, MA) and Camino (Integra Neurosciences, Plainsboro, NJ). ICP was treated if sustained at > 20mmHg, although there was a tendency to lower this threshold in patients < 2 years old. If ICP was elevated, head CT scanning was performed to ensure that there had been no late development of intracranial haematomas or hydrocephalus. The management protocol for elevated ICP was influenced by the underlying pathophysiology, and where possible took into account concurrent PbtO2, PaCO2, CPP, TCD flow velocities and status of AR. Intracranial hypertension despite the above conservative measures was managed with increased sedation, neuromuscular blockade, ventriculostomy (if possible), controlled moderate hyperventilation, and/or hyperosmolar therapy (5% saline and/or mannitol) in a stepwise fashion.

Controlled moderate hyperventilation (PaCO2 28 to 30mmHg) was used rarely, in accordance with published guidelines [5], and only for brief periods as a second-tier therapy to break spikes of

intracranial hypertension. Its use was controlled by PbtO2 (employed only if PbtO2 was greater than 20mmHg) and TCD. No patient underwent severe or prolonged hyperventilation. If significant transcranial TCD or PbtO2 changes occurred at lower PaCO2 levels, PaCO2 was returned to approximately 34 to 35 mmHg. Hypertonic saline was used to treat elevated ICP if the serum sodium was < 155 mmol/L. Thiopentone was used for elevated ICP refractory to conventional medical treatment if the patient's BP was stable. Propofol was not used because of the concerns of adverse effects in children, including fatal lactic acidosis [9, 418]. DCH was used as a second-tier therapy for patients with refractory elevated ICP who did not respond to thiopentone or for rapidly deteriorating ICP control where ICP increased to ≥ 40mmHg or BP was too unstable for thiopentone. For DCH a unilateral large skin flap was turned, hemicraniectomy was performed and the dura was enlarged with a pericranial graft. The bone was stored in a bone fridge in a sterile manner and replaced preferably within 4 to 6 weeks, but occasionally up to 3 months later depending on the patient's clinical condition. Hypothermia was not used.

CPP Management

CPP was calculated as MAP minus ICP (CPP=MAP-ICP). Management of CPP was based broadly on the paediatric guidelines [8], which recommended maintaining CPP > 50mmHg as an option, although recognising that CPP may represent a continuum based on the age of the patient. A more conservative approach was used for children < 2 years old for whom CPP of 45 mmHg was tolerated if PbtO2 was > 20mmHg. In general, the approach to CPP management was influenced by the prevailing ICP and PbtO2 values for the patient, as well as TCD and AR testing results where these were available. CPP was managed first by ensuring the patient was euvolaemic. If not, intravenous isotonic crystalloids were infused until an adequate volume status was obtained. Volume status was assessed by clinical examination, urine output, heart rate, central venous pressure and BP. If the patient was euvolaemic, noradrenalin or dopamine was used to elevate MAP.

If PbtO2 was low despite CPP > 50mmHg, one of the methods employed to improve PbtO2 was elevation of CPP by 5 to 10 mmHg. This was tested against the PbtO2 and ICP response. If the

augmented CPP failed to benefit PbtO2 or caused elevation of ICP, as with impaired AR, this was discontinued.

PbtO2 Management

PbtO2 was measured with Licox catheters (Integra Neurosciences, Plainsboro, NJ), which were inserted into normal-appearing (on head CT) right frontal white matter if there were no localised lesions. In selected cases, catheters were placed in tissue considered to be at risk for ischaemia, which included normal-appearing regions surrounding contusions, near an area of existing hypodensity, or in the hemisphere with more marked swelling. The position of the monitor was confirmed on follow-up head CT. An initial FiO2 challenge confirmed that the probe was functioning adequately [312]. Compromised (low) PbtO2 was defined as less than 20 mmHg and was treated using a hierarchical treatment algorithm in a cause-directed fashion. This meant that at all times a cause for low PbtO2 was searched for and addressed where possible. In the absence of detecting a specific cause the following specific measures were used depending on ICP, MAP, PaO2, Hb, PaCO2, TCD flow velocities and status of autoregulation (when known): 1) elevated or borderline ICP was treated more aggressively if present, 2) the patients BP was elevated to test PbtO2 at a higher CPP with volume infusion and/or inotropic support unless loss of AR caused concomitant increases in ICP with elevated BP, 3) higher PaCO2 was tolerated to induce cerebral vasodilation if ICP was not elevated, 4) blood was transfused to increase Hb to ≥ 10 g/dl, and 5) the inspired fraction of oxygen (FiO2) was increased as an emergency temporary measure or if PbtO2 remained low despite optimisation of the above parameters.

Ventilatory Management

Patients remained intubated and ventilated for the duration of intracranial monitoring. Ventilation was adjusted to maintain SaO2 > 95% and PaO2 approximately 100mmHg (~13kPa). PaCO2 was maintained in general between 30-35 mmHg (~4 to 4.7kPa) unless changes in ICP or PbtO2

prompted temporary adjustment. Tracheostomy was performed if extubation was expected to be delayed (in general after 1 week).

Chapter 10

Summary of Results for Clinical, Demographic, Physiologic data and Outcome

Introduction

This section reports the results of the 52 children with severe TBI, who represent the main cohort, for demographic and clinical characteristics, physiological (ICP, CPP, PaO2, SaO2) factors, treatment factors, and outcome. TCD and AR results are reported separately in their respective sections (Chapter 18 and 19) because they represent a smaller number of patients nested within this group because of selection criteria.

Methods

These results pertain to all children with TBI who underwent ICP, CPP, and PbtO2 monitoring during the period June 2006 to May 2008. Data collection was as specified in Chapter 8. To avoid skewed analysis and biased results, data recorded during terminal periods of patients who died were excluded. Terminal data were defined as those collected after a patient had fulfilled brain death criteria. For patients who received monitoring with PbtO2, ICP and CPP, a total of 5619 hours of recorded data were analysed. Missing or artefactual data for continuously monitored variables accounted for 1.9% of this total.

Demographic and Clinical Data

Baseline demographic and clinical variables on admission are summarised in Table 1.

Table 1: Admission clinical characteristics (N=52 patients)

Characteristic	Value
Age	6.5 ± 3.4 years (9 months-14 yrs old)
Gender (M/F)	39/13 (75% / 25%)
Initial GCS	5 ± 1 (3-8)
GCS 3	5
GCS 4	9
GCS 5	12
GCS 6	10
GCS 7	11
GCS 8	5
Motor component of GCS (median, range)	3 (1-5)
Pupil reaction on admission	
Bilaterally reactive	41 (78.8%)
Unilaterally nonreactive	5 (9.6%)
Bilaterally nonreactive	6 (11.5%)
PTS (median, range)	3.5 (-1 to 5)
PIM 2 score	0.16 ± 0.2
CT classification (initial) I	3 (5.8%)
II	31 (59.6%)
III	13 (25%)
IV	3 (5.8%)
Evacuated mass lesion	2 (3.8%)
Non-evacuated mass lesion	0
Initial hypoxia (number, %)	14 (26.9%)
Initial SBP<90mmHg (number, %)	13 (25%)
Initial MAP (mmHg)	76 ± 19

Values are expressed as mean ± SD (or median and range where specified) or as numbers and proportions.

Age Distribution

The distribution within age groups was: <2 years (n=5, 9.6%), 2-3 years (n=9, 17.3%), 4-7 years (n=20, 38.5%), 8-11 years (n=16, 30.8%), and 12-14 years (n=2, 3.8%). There were 39 boys (75%) and 13 girls.

Mechanisms of Injury

Mechanisms of injury were: motor vehicle accident-related in 40 (76.9%), crush injury in 3 (5.8%), gunshot wound in 4 (7.7%), blunt assault in 2 (3.8%), fall from a height in 1 (1.9%), stab to the head in 1 (1.9%), and non-accidental injury (shaken baby syndrome) in 1 (1.9%). Penetrating injury accounted for 9.6% of cases (n=5). Twenty patients (38%) presented with polytrauma).

Early Insults

Thirteen patients (25%) experienced an initial SBP < 90mmHg and 14 (26.9%) experienced initial systemic hypoxia (SaO2<90% or PaO2<60mmHg) before or on admission to the hospital.

Time Frames

The median time to start of PbtO2 monitoring was 9 hours (IQR 7-17 hours) after injury. Monitoring was started ≤ 12 hours after injury in 34 patients (65%), between 13 and 24 hours in 13 patients (35%), and > 24 hours after injury in 5 patients (9.6%). The length of stay in the ICU was 7.7 ± 4.3 days (range 1 to 19 days), and duration of monitoring was 5.3 ± 3.1 days (range 1 to 15 days).

Physiological Results

Table 2 and 3 summarise the results for general analysis of variables and analysis of abnormal values for important variables respectively. There were no complications associated with PbtO2 or ICP monitoring. Technical problems were encountered with 2 ICP monitors that required replacement. There were no technical problems encountered with the PbtO2 monitors. PbtO2 was monitored close to an area of contusion (but not within the contusion) in 5 cases, and in 2 locations in the same patient in 3 patients.

Table 2: Summary of physiologic monitored variables for total monitored time (5619 hours, terminal data excluded)

Characteristic	Value
PbtO2 (mmHg)	32.9 (25.1-42.3) range 0-128
MAP (mmHg)	(73-91) range 35-140
ICP (mmHg)	14 (12-16) range 0-76
CPP (mmHg)	67 (58-77) range 0-126
PaO2 (kPa)	17.6 (12.7-25) range 5.6-67
PaCO2 (kPa)	4.5 (4-5.1) range 2.7-8.5
SaO2 (%)	99 (98-99) range 30-100
FiO2 (%)	40 (35-55) range 21-100
Haemoglobin (g/dl)	10.1 (9.3-11.1) range 6-14.6
Serum sodium (mmol/L)	143 (140-146) range 131-156
PbtO2/PaO2 (%)	23 (16-34) range 1.7-67

Values are expressed as median (IQR) and range.

Table 3: Abnormal values for physiological variables (N=5619 hours, terminal data excluded) [Refer to Chapter 8 for guide to the variables in the table]. Values are expressed as median (IQR) and range of the values or number of episodes above or below thresholds for all patients, as well as the number of patients (%) who experienced values above or below the respective thresholds as appropriate.

Characteristic	Value
PbtO2	
$PbtO2_{low}$	9.7 (6.4-16.8) range 0-28.3
PbtO2<5 (episodes)	0 (0-0) range 0-20
Number of patients (PbtO2<5)	11 (21%)
PbtO2<10 (episodes)	1 (0-2) range 0-22
Number of patients (PbtO2<10)	26 (50%)
$mPbtO2_{24}$ (mmHg)	28.3 (22.3-34.8) range 0.6-53
ICP	
ICP_{peak} (mmHg)	31 (22-44) range 9-76
$mICP_{24}$ (mmHg)	14 (11-18) range 3-60
$mICP_{total}$ (mmHg)	14 (12-16) range 3-60
ICP>20	6 (1-25) range 0-128
Number of patients (ICP>20)	43 (83%)
mICP>20 (mmHg)	24 (22-27) range 0-61

CPP	
CPP_{low} (mmHg)	43 (33-50) range 0-73
CPP<40	0 (0-2) range 0-24
Number of patients (CPP<40)	20 (38%)
CPP<50	3 (0-12) range 0-77
Number of patients (CPP<50)	58 (73%)
PaO2	
PaO2<8 (episodes)	0 (0-0) range 0-16
Number of patients (PaO2<8)	12 (23%)
$PaO2_{low}$ (kPa)	10.4 (8.4-13) range 5.5-38.3
SaO2	
SaO2<90 (episodes)	0 (0-1) range 0-9
Number of patients (SaO2<90)	18 (35%)
Hb	
Hb_{low} (g/dl)	8.8 (7.9-9.3) range 6-13.6

Values are expressed as median (IQR) and range.

Values for mICP, $mICP_{24}$ and ICP_{peak} (median, IQR) were 14 mmHg (12-16), 14 mmHg (11-18) and 31 mmHg (22-44) respectively. Episodes of ICP > 20mmHg occurred in 43 patients (83%). Median lowest CPP was 43 mmHg (33-50). Despite aiming for CPP targets, episodes of CPP < 40mmHg occurred in 20 patients (38%) and episodes of CPP < 50 mmHg occurred in 58 patients (73%). Mean PbtO2 (excluding terminal data) was 34 ± 13 mmHg (median 32.9mmHg, IQR 25-42). Despite aiming for PbtO2 > 20mmHg, episodes of PbtO2 < 10mmHg occurred in 26 patients (50%) and PbtO2 < 5mmHg occurred in 11 patients (21%). The medians for the lowest PbtO2 and $mPbtO2_{24}$ were 10 mmHg (6-19) and 28mmHg (22-35) respectively.

Treatment Factors

Of the 52 patients, 7 patients underwent DCH (13%) for diffuse brain swelling. Ten patients (19%) received thiopentone. Thirty-six patients (69%) received a RBCT, 31 (59.6%) received inotropes, and 40 (77%) received HTS (to increase serum Na or to treat elevated ICP). These frequencies refer only to patients who underwent PbtO2 monitoring.

Discussion

This cohort of children represents a reliable sample of paediatric patients with severe TBI (median GCS of 5, mean age of 6.5 years old). Pupillary abnormalities on admission were seen in 21% of patients and 38% were polytrauma patients. Penetrating injury is unusual in the paediatric population, but accounted for almost 10% in this group.

Abnormalities in monitored variables were frequent in these patients. Prehospital low BP and hypoxic insults each occurred in about one quarter of the patients. Despite targeting thresholds for ICP, CPP, ventilation and PbtO2, perturbations of these variables were common. Hypoxic episodes while in the

ICU occurred in 23 to 35% (low PaO2 and low SaO2 respectively) of these patients. Episodes of ICP elevation above 20mmHg occurred in more than 80% of patients. CPP decreased on occasion to less than 50mmHg in almost three quarters of the patients, and to less than 40mmHg in more than one third. Half of all patients experienced episodes when PbtO2 dropped to < 10mmHg and just over 20% experienced episodes of PbtO2 < 5mmHg.

These data confirm the frequency of secondary insults in children with severe TBI and provide the background for analysis in the following chapters.

Chapter 11

Associations between Clinical and Physiological Variables, Particularly PbtO2, and Outcome in Children with Severe TBI

Introduction

The goal of neurosurgical and critical care management of children with severe TBI is to avoid or ameliorate secondary injury to maximise the chance of a favourable outcome. Guidelines have been published which aim to direct TBI management protocols based on available evidence [4]. These emphasise adequate resuscitation of the patient, evacuation of intracranial haematomas, control of ICP, maintenance of CPP, and avoidance of secondary systemic insults. However, most recommendations were set at the level of an option because evidence from available studies was weak. Fewer studies are performed in paediatric TBI compared to adults and management difficulties, particularly with regard to defining thresholds for treatment, are compounded by changing physiological norms with age.

A key strategy in neurocritical care is the supply of oxygen to the brain to prevent cerebral hypoxia/ischaemia. Strong evidence from post-mortem [128] and clinical studies [35, 64, 273] suggests that secondary brain hypoxia-ischaemia contributes significantly to poor outcome. However, adherence to physiological targets for ICP control, CPP management and respiratory function may not avoid cerebral hypoxia (Chapter 13). PbtO2 monitoring is being increasingly used to obtain additional information to guide therapy in patients with TBI. Studies in adults have confirmed the relationship between low PbtO2 and poor outcome, but only 2 studies have examined PbtO2 in children (Chapter 6). These both involved small samples (5 and 16 patients respectively). In addition, the relationship

between PbtO2 and other physiological markers in paediatric TBI has not been studied. Therefore, this study aims to examine 1) the relationship between physiologically monitored variables, and in particular PbtO2, and outcome in a large group of paediatric patients with severe TBI, and 2) the relationships between PbtO2 and other physiological variables in paediatric severe TBI.

Methods and Materials

Patient selection and Data Collection

Data from a consecutive series of paediatric patients who underwent PbtO2 and ICP monitoring for severe TBI at Red Cross Children's Hospital from June 2006 to May 2008 were prospectively collected. The procedures for patient selection, initial assessment and stabilisation, general management, physiological data collection, and outcome assessment were summarised in Chapter 8. Results for demographic, clinical, physiological and treatment variables in this cohort of patients are reported in Chapter 10. This chapter examines the associations between several variables and indices of PbtO2 and the associations between these variables and clinical outcome. Outcome was examined as described in Chapter 8. Specifically, associations with overall mortality, GOS and PCPCS were examined.

Statistical Analysis

Spearman's correlation coefficients were used to test correlation between PbtO2 and other physiological variables. Relationships between clinical and physiological variables and outcome were examined with the Wicoxons rank sum test for continuous variables and Pearsons X^2 test for categorical variables. Variables with significant relationships in univariate analysis were entered into a stepwise multivariate logistic regression model. Separate models were constructed for individual PbtO2 parameters. Values were examined as continuous and categorical variables. Regression models were constructed separately for GOS (dichotomised into favourable and unfavourable outcome) and mortality. Further regression analysis was performed on all PbtO2 variables to derive

optimal binary splitting to examine thresholds of PbtO2 as categorical variables. Results are reported as Odd's ratios and confidence intervals (CI) for unfavourable outcome and death respectively. Significance was set at p=0.05. Descriptive statistics are reported as mean±SD or median and interquartile range (IQR).

Results

Data from 52 children with severe TBI who received monitoring for ICP, CPP and PbtO2 between June 2006 and May 2008 were analysed.

Associations Between Other Variables and PbtO2

The Spearman's correlation coefficients and corresponding p-values for the associations between PbtO2 parameters ($PbtO2_{low}$, PbtO2<5, PbtO2<10 and $mPbtO2_{24}$) and all clinical, physiological and treatment variables are shown in Table 1. No single variable was significantly associated with all PbtO2 parameters, but individual associations were found with initial GCS (PbtO2<5, p=0.0113), PTS (PbtO2<10, p=0.0175), mICP>20 ($mPbtO2_{24}$, p=0.0377), CPP_{low} ($PbtO2_{low}$, p=0.0065), CPP<40 ($PbtO2_{low}$, p=0.0269; PbtO2<5, p=0.0212), PaO2<60 ($mPbtO2_{24}$, p=0.0037), SaO2<90 ($PbtO2_{low}$, p=0.0438), use of inotropes ($PbtO2_{low}$, p=0.0276; PbtO2<10, p=0.0277; p=$mPbtO2_{24}$).

Table 1: The Spearman's correlation coefficients (p-value) of each variable with PbtO2 parameters

	$PbtO2_{low}$	PbtO2<5	PbtO2<10	$mPbtO2_{24}$
Initial GCS	0.21 (0.1404)	-0.35 (0.0113)*	-0.26 (0.0625)	0.03 (0.8545)
Motor GCS	0.17 (0.2307)	-0.11 (0.4576)	-0.21 (0.1378)	0.14 (0.3279)
Gender	-0.15 (0.2903)	0.002 (0.9887)	0.15 (0.2829)	-0.20 (0.1495)
Age	0.21 (0.1429)	-0.01 (0.9327)	-0.01 (0.9276)	0.041 (0.7748)
PTS	-0.15 (0.2817)	0.10 (0.4709)	0.33 (0.0175)*	-0.08 (0.566)
PIM 2	-0.07 (0.6208)	0.11 (0.4568)	0.07 (0.6012)	-0.09 (0.5321)
CT class	-0.07 (0.6286)	0.09 (0.5474)	-0.02 (0.8974)	0.04 (0.7652)
ICP>20	-0.09 (0.5105)	0.02 (0.8658)	0.06 (0.6641)	0.05 (0.7091)
mICP>20	0.03 (0.8592)	0.07 (0.604)	-0.04 (0.7821)	0.29 (0.0377)*
ICPpeak	-0.09 (0.4897)	0.11 (0.4421)	0.09 (0.5087)	0.15 (0.296)
$mICP_{24}$	-0.18 (0.1989)	0.21 (0.1258)	0.14 (0.3294)	0.16 (0.2518)
mICP	-0.18 (0.2121)	0.19 (0.1876)	0.12 (0.396)	0.15 (0.2801)
CPPlow	0.38 (0.0065)*	-0.26 (0.0641)	-0.27 (0.054)	0.06 (0.6512)
CPP<40	-0.31 (0.0269)*	0.32 (0.0212)*	0.19 (0.1702)	-0.09 (0.5394)
CPP<50	-0.23 (0.1093)	0.10 (0.4683)	0.1 (0.3227)	-0.07 (0.6211)
Pupils	-0.24 (0.0833)	0.23 (0.108)	0.22 (0.1236)	0.017 (0.9074)
Initial hypoxia	0.03 (0.8548)	0.07 (0.6193)	0.01 (0.9481)	0.08 (0.5686)
Initial MAP	-0.01 (0.948)	-0.07 (0.6087)	0.08 (0.5577)	-0.07 (0.6011)
Initial SBP<90	-0.01 (0.9171)	0.02 (0.9101)	-0.04 (0.7724)	-0.02 (0.8923)
Initial Hb	0.04 (0.8021)	-0.04 (0.77)	0.05 (0.6994)	-0.06 (0.6498)
Polytrauma	0.05 (0.7315)	0.05 (0.7342)	-0.02 (0.882)	-0.11 (0.4349)
PaO2<60	-0.22 (0.1193)	0.25 (0.0789)	0.20 (0.1463)	-0.40 (0.0037)*
PaO2low	0.06 (0.6541)	0.01 (0.9495)	-0.04 (0.7602)	0.26 (0.0618)
mPaO2	-0.24 (0.0841)	0.26 (0.0584)	0.14 (0.318)	-0.01 (0.9559)
SaO2<90	-0.28 (0.0438)*	0.27 (0.0544)	0.27 (0.0569)	-0.20 (0.1616)
Hb_{low}	0.09 (0.5409)	-0.18 (0.1943)	-0.03 (0.8292)	0.09 (0.5238)
mHb	-0.16 (0.268)	0.01 (0.9209)	0.07 (0.629)	-0.13 (0.3641)
Duration.	-0.04 (0.8249)	-0.05 (0.7139)	0.041 (0.7753)	-0.15 (0.2728)
RBCT	-0.08 (0.5951)	0.12 (0.3733)	-0.02 (0.9113)	-0.18 (0.2038)
HTS	-0.16 (0.2537)	0.041 (0.7758)	0.11 (0.426)	-0.14 (0.3254)
DCH	-0.05 (0.7076)	-0.10 (0.465)	0.13 (0.3411)	0.07 (0.6168)
Thiopentone	0.07 (0.6387)	-0.16 (0.2477)	0 (1)	-0.13 (0.3581)
Inotropes	-0.31 (0.0276)*	0.10 (0.461)	0.31 (0.0277)*	-0.31 (0.0276)*

Table 1: Spearman's correlation coefficients (p-values) for associations between PbtO2 parameters and clinical, physiological and treatment variables. Significant results are highlighted with an asterisk (*). **CT class**, CT classification; **Duration**, length of invasive monitoring; **HTS**, hypertonic saline (number of times used in each patient); **Thiopentone,** use of thiopentone for ICP control; **DCH**, decompressive craniectomy used (included craniectomy for mass lesion removal in one patient); **Inotropes**, use of inotropes to increase BP.

Outcome

Overall mortality was 9.6% (n=5). Of the patients who died, 3 died while in ICU (all died within 24 hours of sustaining head injury), and 2 died after discharge to the ward. All deaths occurred in hospital and within 30 days of injury (median 2 days after injury, range 1-26). Of the 3 patients who died within 24 hours of admission, one patient had an intra-abdominal haemorrhage and experienced a cardio-respiratory arrest before admission to the ICU. Although the patient was successfully resuscitated initially, she underwent progressive ICP increase with PbtO2 compromise within hours of the arrest. The other 2 early deaths were both related to exsanguinating haemorrhage from large base of skull fractures with likely intracranial carotid injuries. The 2 late deaths both appeared to be related to respiratory complications that developed after initial aspiration at the scene of the injury.

Moderate to severe disability was present at follow-up in 7 of the survivours. Therefore, overall outcome was unfavorable (GOS 1-3) in 12 patients (23%) and favorable (GOS 4-5) in 40 (77%). Dichotomised outcome results were the same between GOS and PCPS; therefore, further analysis was performed with the GOS. There were no vegetative survivors. Mean duration of follow-up for survivors was 10.9 ± 5.4 months (range 3-22 months).

Univariate Analysis of Relationships with Outcome

The relationships between outcome as the dependent variable and clinical, physiological and treatment variables are summarised in Table 2. For ease of use, only the Spearman's p-values are included in the table; however, results for the Spearman's test was similar to those obtained with the appropriate Pearson's, Wilcoxon's and X^2 tests. Variables that had significant relationships with unfavorable outcome included: (Wilcoxon's and X^2 p-values) initial GCS (p=0.0011), CT classification (p=0.0253), ICP_{peak} (p=0.0189), $mICP_{24}$ (p=0.022), mICP (p=0.0344), CPP_{low} (p=0.0259), CPP<40 (p=0.0328), pupil reactivity (p=0.0044), $PbtO2_{low}$ (p<0.0001), PbtO2<5 (p<0.0001), PbtO2<10 (p<0.0001), $mPbtO2_{24}$ (p=0.0219), and Time-Hypoxia product (p<0.0001).

In univariate logistic regression analysis all the above variables were still significant. Additional variables that were significant were PIM 2 (p=0.026) and mean PaO2 (co-efficient 0.047).

PbtO2<10mmHg occurred in 40% (n=16) of patients who had a favorable outcome and in 92% (n=11) of patients who had an unfavorable outcome. PbtO2<5mmHg occurred in 10% (n=4) and 67% (n=8) in these groups respectively. $mPbtO2_{24}$ was 30.4 ± 8.9mmHg in patients with favorable outcome and 21.9 ± 16.4mmHg in patients with unfavorable outcome. PbtO2 decreased to 0mmHg in all patients who developed brain death while being monitored (n=3).

Univariate Analysis of Relationships with Mortality

Significant relationships with mortality included initial GCS (p=0.0011), pupils (p=0.0016), mean PaO2 (0.0052), $PbtO2_{low}$ (p=0.0032), PbtO2<5 (p<0.0001), PbtO2<10 (p<0.0001), and Time-Hypoxia product (p=0.0012). In univariate logistic regression analysis all of these variables remained significant, while in addition the following were also significant: PIM 2 (p=0.012), ICP_{peak} (p=0.037), $mICP_{24}$ (p=0.013), CPP_{low} (p=0.027), and $mPbtO2_{24}$ (p=0.048).

Table 2: Comparison of variables between 2 groups for clinical outcome (GOS dichotomised). Values are expressed as median (interquartile range) or number (percentage).

Variable	Favorable (n=40)	Unfavorable (n=12)	Coefficient	*P*-value
Patient age [years]	6 [5-7]	5.8 [3.3-8.1]	-0.06	0.6914
Gender (male)	1 [1-1]	1 [1-1]	0.00	1.0000
Initial GCS	6 [5-7]	4 [3-5]	-0.46	0.0006*
Motor GCS	3 [3-4]	3 [2-4]	-0.23	0.0941
Polytrauma (freq)	15 (37.5%)	5 (41.6%)	0.04	0.7995
PTS	3.5 [2-4]	3.5 [3-4]	0.10	0.4653
PIM2	0.07 [0.1-0.1]	0.13 [0.1-0.6]	0.20	0.1474
ICP>20	5 [1-22]	22.5 [13.2-28]	0.21	0.1367
mICP>20 [mmHg]	24 [22-26.8]	25.5 [24-32]	0.22	0.1217
ICP_{peak} [mmHg]	29 [22-40]	47 [32-55]	0.33	0.0168
$mICP_{24}$ [mmHg]	14 [11-16]	20 [13-29]	0.32	0.0198
$mICP_{total}$ [mmHg]	13 [11-15]	17 [12-20]	0.30	0.0320
CPP_{low} [mmHg]	44 [35-51]	29 [20-45]	-0.31	0.0236*
CPP<40	0 [0-1]	3 [0-10]	0.30	0.0304*
CPP<50	3 [0-8.8]	8 [2-18.5]	0.21	0.1366
Pupils	1 [1-1]	2 [1-3]	0.40	0.0032*
Initial hypoxia	0 [0-0]	0 [0-1]	0.08	0.5770
Initial MAP [mmHg]	78 [69-89]	71 [67-93]	-0.03	0.8556
Initial SBP<90	0 [0-1]	0 [0-0]	-0.11	0.4570
Initial Hb [g/dl]	10 [9-11]	10.5 [9.6-11]	0.02	0.8636
PaO2<8	0 [0-0]	0 [0-1]	0.24	0.0901
$PaO2_{low}$ [kPa]	10.6 [8.5-13]	9 [7.9-12.2]	-0.07	0.6146
mPaO2 [kPa]	19.5 [17.5-22.9]	23.2 [18.8-25.9]	0.22	0.1162
Hb_{low} [g/dl]	8.8 [8-9.4]	8.8 [7.8-9.1]	-0.1	0.4852

mHb [g/dl]	9.8 [9.4-10.9]	10.4 [9.8-10.7]	0.14	0.3167
SaO2<90 (episodes)	0 [0-1]	1 [0-2]	0.25	0.0787
$PbtO2_{lowest}$ [mmHg]	13.6 [7.3-17.8]	3.6 [0.2-8.8]	-0.49	0.0002*
PbtO2<5 (episodes)	0 [0-0]	1 [0-8.5]	0.59	<0.0001*
PbtO2<10 (episodes)	0 [0-1]	4 [1.8-13.8]	0.55	<0.0001*
$mPbtO2_{24}$[mmHg]	31.1 [26.6-35]	20.8 [11.4-27.8]	-0.32	0.0197*
Time-Hypoxia prod	0 [0-2.8]	20.5 [2.6-75.1]	0.52	0.0001*
Monitoring length (hrs)	109 [63-153]	138 [93-184]	0.10	0.4789
HTS (number given)	4 [0-9]	3 [2-8]	0.04	0.7542
RBCT (freq)	24 (60%)	10 (83%)	0.21	0.1416
Inotropes (freq)	22 (55%)	9 (75%)	0.17	0.2235
Thiopentone (freq)	7 (17.5%)	3 (25%)	0.08	0.5721
DCH (freq)	4 (10%)	4 (33%)	0.27	0.0507

Table 2: Comparison of clinical and physiological variables between patients who had favorable (n=40) and unfavorable (n=12) outcomes. **Coefficient**, Spearman's correlation coefficients for the association between the variable and outcome with the corresponding *p*-values (similar results were found with Wilcoxons rank sum test and Pearson's X^2). Asterisks (*) denote significant results. **Time-Hypoxia prod**, product of depth and duration of hypoxia (see text); **CT class**, CT classification; **Duration**, length of invasive monitoring; **RBCT**, red blood cell transfusion; **HTS**, hypertonic saline (number of times used); **Thiopentone,** use of thiopentone for ICP control; **Inotropes**, use of inotropes to increase BP.

Multivariate analysis

Outcome (GOS): Variables that were entered into multivariate models included age, initial GCS, CT classification, ICP_{peak}, CPP_{low}, pupil reactivity, PaO2<60 and all of the PbtO2 parameters. Age was forced into the model because of its clinical importance. All PbtO2 variables had significant relationships with outcome in multivariate analysis (Table 3). $mPbtO2_{24}$ had a marginal relationship with outcome when analysed as a continuous variable (p=0.048) but not when analysed as a dichotomised variable (dichotomised at 16mmHg, p=0.062). Significant associations with outcome were also found for initial GCS, CT classification, ICP_{peak}, and CPP_{low} when tested in multivariate models with some, but not all PbtO2 parameters. Table 4 summarizes the adjusted Odd's ratios for the multivariate results of PbtO2 parameters examined as dichotomised variables with outcome as the dependent variable.

Table 3: PbtO2 parameters (as dichotomous values) with adjusted Odd's ratios for unfavorable outcome from multivariate logistic regression models

Parameter	*P*-value	OR	Confidence Interval	R^2
$PbtO2_{low}$<5mmHg	0.004*	24.6	2.8-214.6	0.561
PbtO2<5 for >1 hour	0.015*	27.4	1.9-391	0.54
PbtO2<10 for >2 hours	0.021*	10.8	1.4-82.4	0.563
$mPbtO2_{24}$<16mmHg	0.062	8.9	0.9-87.5	0.521
Time-Hypoxia product>20	0.002*	47.6	4.2-543.6	0.564

P-values, adjusted Odd's ratios (OR), confidence intervals and Nagelkerke's R^2 for each multivariate model (other variables not shown). Odds ratios are reported as the Odds of unfavorable outcome.

Mortality: Variables that remained in the final multivariate model included initial GCS, mICP, CPP_{low}, pupil reactivity and the PbtO2 parameters. PbtO2 parameters were independently associated with mortality in multivariate analysis. No other variables were independently associated with mortality when tested in models with PbtO2 parameters. Table 4 displays the multivariate results for dichotomised PbtO2 parameters tested with mortality as the dependent variable.

Table 4: PbtO2 parameters (as dichotomous values) with adjusted Odd's ratios for mortality from multivariate logistic regression models

Parameter	*P*-value	OR	Confidence Interval	R^2
$PbtO2_{low}$ <5mmHg	0.016*	26.9	1.9-387.4	0.464
PbtO2<5 for >1 hour	0.005*	26.8	2.7-265.0	0.33
PbtO2<10 for >2 hours	0.017*	20.4	1.7-244.7	0.442
$mPbtO2_{24}$<16mmHg	0.012*	25.8	2.1-323.9	0.439
Time-Hypoxia product>20	0.002*	43.3	3.8-491.3	0.453

P-values, adjusted Odd's ratios (OR), confidence intervals and R^2 for each multivariate model (other variables not shown). Odds ratios are reported as the Odds of unfavorable outcome.

Discussion

In this study we examined relationships between clinical, physiological and treatment factors, and in particular PbtO2, and outcome in 52 children with severe TBI. The main findings were: 1) Low PbtO2 is an independent factor associated with mortality and unfavourable outcome (GOS 1-3) in children with severe TBI, 2) PbtO2 was significantly less and for a longer duration of time in patients with poor outcome, 3) other parameters such as initial GCS, CPP, and ICP had a variable relationship with PbtO2.

Methodological Limitations

There are several potential limitations to this study. First, the sample size is small; however, it is relatively homogeneous because it includes only children with severe TBI who were less than 15 years old. Second, the age range (9 months old to 14 years old) represents wide differences in physiological thresholds. Ideally, a larger number of patients in each age category should be examined separately as there may be age-related differences in thresholds that may be tolerated. However, few institutions treat large enough numbers of children with severe TBI for this to be accomplished easily in single-centre studies. In this study age was included in all multivariate models to control for its effect on the association of different variables with outcome, and the associations between different variables and PbtO2. Third, outcome evaluation in children is difficult and paediatric neuropsychological testing was not performed in this study. However, the GOS and PCPCS used in this study can be dichotomised easily to enable examination for associations with death and severe disability. These outcome assessments are used commonly in paediatric TBI, are practical, and allow for comparison with other studies. Fourth, this was not a pure observational study in that interventions were directed at low PbtO2. Untreated low PbtO2 may have different associations with other variables and outcome parameters. Fifth, even though PbtO2 is associated with outcome, the effect of interventions for low PbtO2 were not examined; therefore no comment can be made on which methods may be effective, what their adverse effects are, and what impact these may have on

outcome. Finally, the PbtO2 data does not contain enough detail to allow a more specific conclusion on what are the key thresholds for PbtO2 that are associated with poor outcome. Despite these limitations, these results show the strong association between low PbtO2 and poor outcome in paediatric TBI and suggest that future studies designed to examine the impact of interventions for low PbtO2 in children would be important.

PbtO2 and Other Physiological Variables

The relationships between other physiological measures and PbtO2 were variable. Significant relationships with low PbtO2 were seen with lowest CPP, episodes of CPP<40mmHg, episodes of PaO2<60mmHg and episodes of SaO2<90%. The association between PbtO2 and measures of arterial oxygenation is not surprising because systemic hypoxia is a known secondary insult that may worsen outcome in TBI [64, 273]. Also, PbtO2 is a measure of oxygen tension; therefore it is influenced by PaO2 [236, 296]. Mean PaO2 was higher in patients who had a poor outcome and particularly, who died. This may reflect higher FiO2 used in unsuccessful attempts to increase low PbtO2 in these patients. A direct relationship between mean PaO2 and mortality is unlikely because inspection of the data reveals the highest PaO2 levels occurred in the patients who died early. Of interest, low PbtO2 was associated with CPP<40mmHg, but not with CPP<50mmHg. The published guidelines of the management of paediatric TBI recommended maintaining CPP above 50mmHg only at the level of an option and age-appropriate CPP may represent a continuum [8]. Of the ICP parameters tested, only mean ICP above 20mmHg had a marginal relationship with mean PbtO2 in the first 24 hours (p=0.04). ICP-directed versus CPP-directed management of patients has been debated but no clear evidence supports either approach as better [278, 294]. Also, the benefits of solely ICP monitor-based therapy have been questioned [79, 81]. Finally, maintaining guidelines-based thresholds for ICP and CPP do not necessarily avoid brain hypoxia (Chapter 13). Therefore, targeting treatment in individuals based on additional measures has been proposed [31, 271, 305].

PbtO2 and Outcome

Indices of low PbtO2 were consistently associated with poor outcome and mortality in multivariate models. Other variables that had relationships with outcome in univariate analysis were initial GCS, pupil reactivity, CT classification, and low CPP. The latter variables were significant in multivariate models for GOS with some, but not consistently with all of the PbtO2 indices. None of these variables had a significant relationship with mortality when included in models with PbtO2 indices. In multivariate models that included initial GCS, pupil reactivity, ICP, CPP and age, low PbtO2 emerged consistently as an independent factor associated with poor outcome and mortality. The likelihood of poor outcome was inversely related to the duration and the depth of the episodes of low PbtO2. If PbtO2 was < 5mmHg for more than 1 hour, the Odd's ratio for poor outcome was 27.4 (CI 1.9-391) and the Odd's ratio for mortality was 26.8 (CI 2.7-265). If PbtO2 was < 10mmHg for more than 2 hours the Odd's ratios for poor outcome and mortality were 10.8 (CI 1.4-82.4) and 20.4 (CI 1.7-244) respectively. These data confirm results from studies in adult patients with TBI in a relatively large group of children with severe TBI.

Conclusion

This study demonstrates a significant relationship between low PbtO2 and measures of poor outcome after paediatric severe TBI (mortality and poor clinical outcome based on the GOS and PCPS), independent of multiple clinical and physiological variables, including age. The overall relationship between low PbtO2 and physiological markers of secondary insults such as ICP, CPP, and PaO2 was variable, but may be significant in individual patients.

Chapter 12

Delayed Cerebral Infarction and Brain Tissue Oxygen Monitoring in Children with Acute Cerebral Injury

Introduction

Note: In this section, results of PbtO2 from patients managed with other clinical conditions during the same time period were included to increase the reliability and generalizability of results. If PbtO2 is related to delayed cerebral infarction, the results should be fairly consistent across different pathologies.

Cerebral infarction is a known complication of acute neurological injury such as TBI and meningitis, and is associated with poor outcome. In TBI for example, clinical studies demonstrate that post-traumatic cerebral infarction (PTCI) is common and may occur in 8 to 19% of adults with moderate or severe TBI [220, 359], although the incidence is lower if patients with mild TBI are included [239]. Post-mortem studies show that brain ischemia is common in patients who die after sustaining TBI [127, 128]. However, these studies have largely examined adult populations and the incidence of PTCI in children is not known. This is important because injury remains the leading cause of death in many parts of the world and children who sustain TBI have the highest mortality (Chapter 1). Similarly, infarction after other neurological disorders e.g. meningitis is common and is associated with adverse outcomes, particularly if children are young or there is a delay in treatment [61, 317, 318, 340]. Furthermore, the immature brain may be less tolerant of hypoxic-ischaemic insults than previously believed [413].

In all forms of acute neurological injury a range of local and systemic mechanisms may be involved in the development of cerebral infarction not present at the time of admission to hospital. These include hypotension, elevated ICP, impaired autoregulation, uncoupling of flow-metabolism matching, focal mass effect, vascular impingement due to herniation, vasospasm, thrombosis, vasculitis, and direct vascular injury [128, 239, 286, 359]. This delayed cerebral infarction (DCI) is at least potentially avoidable; however conventional ICU monitoring may not identify patients at high risk of hypoxic-ischaemic injury or DCI until it is too late to intervene.

PbtO2 monitoring potentially may benefit patients through early detection of hypoxia-ischaemia to enable early intervention. However, there are a number of uncertainties. First, PbtO2 is a measure of local tissue oxygen tension with a microcatheter that samples a volume of brain of only 14-17mm^3 [175, 188]. Therefore, although the PbtO2 monitor may reflect reductions in global perfusion (Chapter 6), it may not exclude focal hypoxia that occurs in other regions of the brain. It follows that the issue of placement of the monitor is important. Second, the interpretation of the PbtO2 reading is subject to some debate. It may be too simplistic to view PbtO2 only as a measure of the balance between supply and demand because it is significantly influenced by the dissolved oxygen in plasma rather than only by arterial oxygen content or local oxygen delivery [296]. Third, the relationship between PbtO2 and DCI in TBI or meningitis has not been defined. Although some information on PbtO2 and cerebral infarction after subarachnoid haemorrhage is available [162, 174], it is less certain whether information from PbtO2 monitors can reliably detect or predict progression to infarction after TBI or meningitis. Therefore, this study examined 1) whether PbtO2 monitoring predicts DCI in children with neurological injury in the ICU, 2) the association of other clinical and physiological parameters with DCI, and 3) the incidence of DCI after severe TBI in children.

Methods and Materials

Patient Selection

Data were extracted from children who underwent PbtO2 monitoring between June 2006 and May 2008. General selection of patients, assessment and management were as summarised in Chapter 8. Specifically, patients were included in the study if 1) they had a PbtO2 monitor, 2) they had follow-up imaging (computed tomography, magnetic resonance imaging or perfusion scan) and 3) the last scan was at least one week after the initial presentation, unless an earlier scan demonstrated obvious infarction (e.g. for patients who died within the first week). Patients who fulfilled brain death criteria or in whom brain death was imminent in the emergency room on admission to the hospital did not undergo monitoring. Patients who were admitted to the ICU but were likely to be extubated early after admission because of improved condition also were not monitored.

Radiological Evaluation of Infarction

In general, head CT scans were performed on admission, after 24 hours, and thereafter when clinically indicated. Initial head CT scans after TBI were graded according to the Marshall classification [223]. Scans of patients with meningitis were examined for the presence of brain edema, hydrocephalus, infective mass lesions and the pattern of contrast enhancement.

To determine if DCI occurred, the original neuroradiology report of all scans for each patient was reviewed and each CT scan was separately examined for brain hypodensities in vascular territories by 2 clinicians, one of whom was a paediatric neuroradiologist. When there was uncertainty, a third reviewer examined the CT scan to reach consensus. All were blinded to the PbtO2 data. Well-circumscribed hypodensities present on follow-up CT scans but not present on the initial CT study were considered to represent DCI. These hypodensities were classified as infarction if they remained present on subsequent scans or were observed on the last scan of patients who subsequently died.

To differentiate ischaemic lesions from posttraumatic contusion after TBI, a hypodense lesion had to be present at 3 weeks or more after injury without signs of resolution [220], or had to be confirmed by post-mortem findings in patients who died before this time and who required a post-mortem examination independently of the study. If there was a hypodensity on the initial scan, DCI was diagnosed only if this hypodensity increased in size or a new hypodensity in a separate anatomical region was detected. DCI was classified [220, 359] as well-demarcated regions of low attenuation conforming to 1) a known arterial vascular distribution (territorial infarction), and 2) a watershed distribution (watershed infarction) that affected boundary zones between major internal carotid or vertebral branches, or in terminal zones of perforating arteries.

Clinical Management

In general patients were managed as previously described. In addition, appropriate antibiotics were administered for meningitis and ventriculostomies were placed for hydrocephalus.

Physiological Variables

The recording of clinical and physiological data was the same as previously documented (Chapter 8).

Statistical Analysis

Data were tested for normality with the Shapiro-Wilk test. Spearman's and Pearson's correlation was used to test the association of individual variables with DCI. Correlation coefficients are reported as r. Differences between the 2 groups (those who developed DCI and those who did not) were further tested with the Wilcoxon rank sum test. Variables with significant relationships were entered into a multiple logistic regression model to test for associations with DCI. Further regression analysis was performed on all PbtO2 variables to derive optimal binary splitting to examine thresholds of PbtO2 as

categorical variables. Significance was set at p=0.05. Data are expressed as mean ± SD or median and interquartile range (IQR).

Results

Sixty-two paediatric patients had PbtO2 monitors between June 2006 and May 2008. Five patients were excluded from analysis because no infarct was documented but their last head CT scan was less than one week after presentation. This left 57 patients in the study. The indications for monitoring and clinical characteristics of the patients are summarised in Table 1. The most common indication for PbtO2 monitoring was severe TBI (n=48; 84%). This was followed by patients with meningitis (n=6, 10.5%). All patients with TBI had severe TBI and all patients with meningitis had severe brain edema (n=1) or acute hydrocephalus (n=5) and were in coma (GCS 3 to 5). Five of the 6 patients with meningitis had tuberculous meningitis (TBM). The mean age for all patients was 6.1 ± 3.5 years. For TBI patients the mean age was 6.4 ± 3.4 years (range 9 months to 14 years) and for patients with meningitis the mean age was 3.8 ± 3.9 years (range 1-5 years).

Table 1: Admission clinical variables characteristics for patients with and without DCI

Characteristic		Value
Pathology		
	TBI	48
	TBM	5
	Bacterial meningitis	1
	Extracranial injury/Shock	1
	Metabolic encephalopathy	1
	Hypoxic injury	1
GCS categories		
	GCS 3	7
	GCS 4	9
	GCS 5	13
	GCS 6	10
	GCS 7	12
	GCS 8	6
Age		6.1 ± 3.5 (range 0.7-14) years
Pupils	- Bilaterally reactive	43
	- Unilaterally nonreactive	6
	- Bilaterally nonreactive	8

Radiological Diagnosis of Delayed Cerebral Infarction

Thirteen patients (22.8%) had radiological evidence for DCI on follow-up head CT scan (8 TBI, 3 TBM, 1 bacterial meningitis, 1 extracranial injury/shock). The median length of time for follow-up imaging (time from admission to last scan) for survivors was 54 days (IQR 19-164). There were 9 deaths (15.8%) in the whole group. All 9 deaths occurred within the first 30 days, and 8 occurred while in the ICU. DCI were documented in 8 (89%) of the patients who died and in 5 (10%) of the survivors. Table 2 lists the distribution of infarcts and PbtO2 probe location. In 2 of the 13 patients with DCI, the infarct was in the hemisphere contralateral to the PbtO2 monitor (Table 2).

Table 2: Distribution of DCI on follow-up head CT scan

Patient	Infarct distribution	Location of monitor
1	Left MCA perforators	Right frontal
2	Right MCA perforator	Left frontal
3	Left MCA, PCA	Left parietal
4	Bilateral ICA	Right frontal
5	Left MCA, ICA	Left frontal
6	Left ACA, PCA	Left frontal
7	Left BG, MCA	Left frontal
8	Bilateral ICA	Right frontal
9	Left MCA	Left frontal
10	Right ACA, MCA; Left MCA perforators	Right frontal
11	Right PCA, Left PCA, MCA perforators	Left frontal
12	Bilateral ICA	Right frontal
13	Bilateral ICA	Right frontal

Incidence of DCI in TBI Patients

The incidence of DCI in TBI patients in this group (who had PbtO2 monitors and met the entry criteria, n=48) was 16.7%. To estimate the incidence of DCI for all patients who were treated for severe TBI during this period we further examined all admissions to the ICU for severe TBI, including those who did not undergo PbtO2 monitoring. Twenty-four patients with severe TBI were also treated in the ICU but were not monitored with PbtO2. Most of these patients had type I or type II Marshall scans and

were extubated early because of an improving level of consciousness; therefore, PbtO2 monitoring was not instituted. The same entry criteria were applied to these patients for inclusion in the study (apart from PbtO2 monitoring). Nineteen of these patients met the entry criteria for evaluation of follow-up imaging and were examined. Of these only one patient, who had experienced non-accidental injury (shaken baby syndrome), developed DCI. All patients in this group survived. Therefore, for the whole group (patients admitted to the ICU with severe TBI in the 2 year period with or without PbtO2 monitoring who had appropriate follow-up imaging (n=67), the incidence of DCI was 13.4%. The remaining results apply only to patients who underwent PbtO2 monitoring.

PbtO2 and DCI

Clinical and physiological variables with the correlation coefficients for each variable and the probability of infarction for the 2 groups (patients with and without DCI on follow-up head CT) are summarised in Table 3. The lowest PbtO2 was ≤ 9mmHg in all patients who developed DCI. Similarly, episodes of PbtO2<10 occurred in all patients (n=13 of 13) with DCI but in only 41% (n=18 of 44 patients) of those who did not. Episodes of PbtO2<5mmHg occurred in 85% (n=11 of 13) and 18% (n=8 of 44) patients with and without DCI respectively. The mean length of time that PbtO2 was <10mmHg in DCI patients was almost 8-fold greater than patients without DCI (12.7 ± 13.2 versus 1.6 ± 3 hours, p<0.0001). The duration of PbtO2<5mmHg was almost 35 times longer in the DCI group (10.4±11.1 versus 0.3±1.2 hours, p<0.0001). The Time-Hypoxia product for the 2 groups is shown in Fig 1.

Table 3: Clinical and physiological variables in patients with and without DCI (expressed as median [interquartile range]). See Chapter 8 for guide to variables in the Table.

Variable	DCI (n=13)	No DCI (n=44)	Coefficient	*P*-value
Initial GCS	3 [3-5]	6 [5-7]	-0.573	<0.0001*
Patient age [years]	5.5 [2-8]	6 [3-9.1]	0.103	0.445
ICP>20	10 [2-21]	5.5 [1-27]	-0.026	0.850
mICP>20 [mmHg]	26 [24-39]	24 [22-26]	0.233	0.081

ICP_{peak} [mmHg]	41 [26-74]	29 [22-40]	0.164	0.223
$mICP_{24}$ [mmHg]	20 [13-39]	14 [11-16]	0.255	0.055
$mICP_{total}$ [mmHg]	14 [12-21]	13 [11-16]	0.177	0.187
CPP_{low} [mmHg]	24 [10-48]	44 [34-51]	-0.329	0.012*
CPP<40	7 [0-14]	0 [0-1.3]	0.275	0.038*
CPP<50	8 [2-18]	3 [0-11.3]	0.142	0.294
Pupils	2 [1-3]	1 [1-1]	0.496	<0.0001*
Initial hypoxia	0 [0-0]	0 [0-1]	-0.060	0.655
Initial MAP [mmHg]	70 [55-87]	69 [79-89]	-0.142	0.291
Initial SBP<90	0 [0-1]	0 [0-0]	0.176	0.192
Initial Hb [g/dl]	8.7 [7-10.5]	10.5 [9-11]	-0.251	0.060
PaO2<8	0 [0-1]	0 [0-0]	0.104	0.439
$PaO2_{low}$ [kPa]	10.2 [7.9-14.5]	10.7 [8.4-13]	0.037	0.785
mPaO2 [kPa]	21.7 [16.2-28.1]	19.6 [17.6-24.7]	0.052	0.700
Hb_{low} [g/dl]	8.7 [7.9-9.8]	8.8 [8.2-9.3]	0.028	0.836
mHb [g/dl]	10.5 [9.8-11.2]	10 [9.5-10.9]	0.158	0.241
SaO2<90	0 [0-2]	0 [0-1]	0.158	0.239
$PbtO2_{lowest}$ [mmHg]	0 [0-1.7]	12.2 [7.2-17]	-0.626	<0.0001*
PbtO2<5	6 [2-16]	0 [0-0]	0.681	<0.0001*
PbtO2<10	6 [4-19]	0 [0-1]	0.646	<0.0001*
$mPbtO2_{24}$[mmHg]	13.3 [3.1-18.6]	28.4 [24.7-34.2]	-0.454	0.0004*
Time-Hypoxia prod	54.6 [28-136]	0 [0-3.25]	0.641	<0.0001*

Comparison of clinical and physiological variables between patients who developed DCI (**DCI**) and those who did not (**No DCI**). **Time-Hypoxia prod**, product of depth and duration of hypoxia (see text). **Coefficient**, Spearman's correlation coefficients for the association between the variable and DCI with the corresponding *p*-values. Asterisks (*) denote significant results.

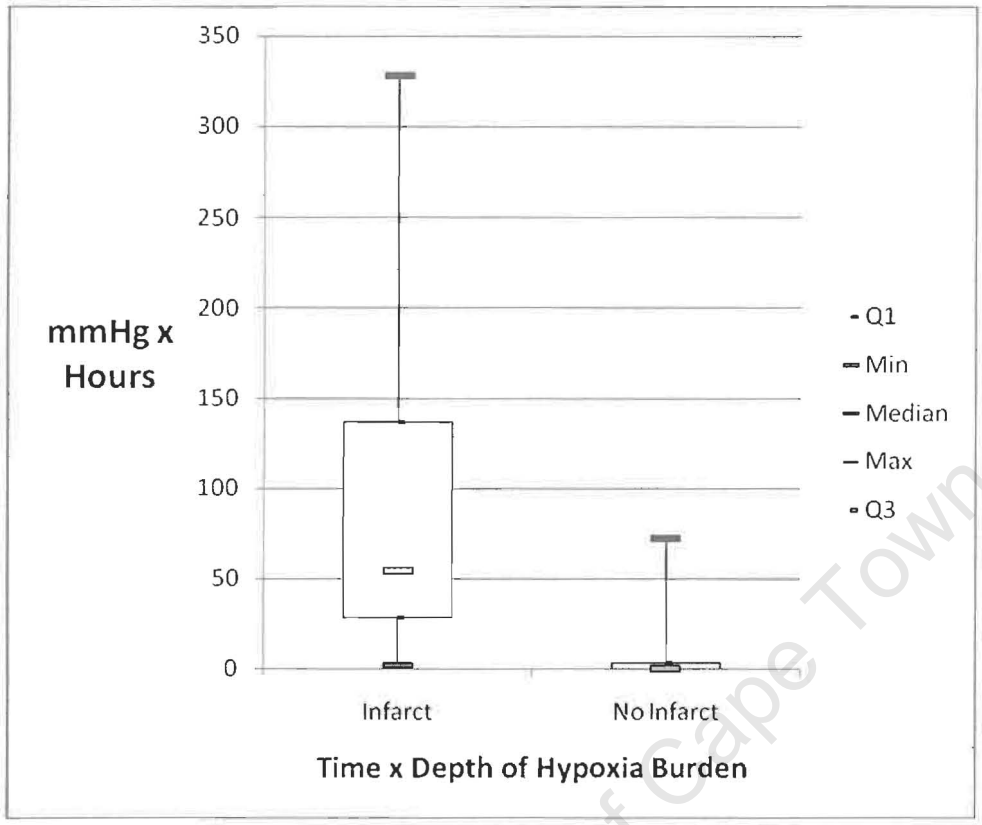

Figure 1: Comparison between patients with and without DCI for the Time-Hypoxia product (Chapter 8) reflecting the burden of brain hypoxic-ischaemic injury (p<0.0001).

Relationship between Physiological Variables and DCI

Variables that had significant relationships with DCI (Table 3) included initial GCS, pupil reactivity, CPP_{low}, CPP<40 and all PbtO2 parameters ($PbtO2_{low}$, PbtO2<5, PbtO2<10, $mPbtO2_{24}$ and Time-Hypoxia product. There was a trend observed for association between ICP and DCI ($mICP_{24}$ [p=0.055] and mICP>20 [p=0.081]) and initial Hb (p=0.06). PbtO2 parameters were then examined with logistic regression to determine the risk of DCI at defined thresholds (Table 4). The Odd's ratios (OR) for DCI and 95% confidence intervals (CI) for specific PbtO2 parameters were as follows: if $mPbtO2_{24}$ was less than 16.5mmHg the OR for infarction was 22.5 (5-107), if a patient experienced

PbtO2<10 for more than 1 hour the OR was 54 (6-477), and if a patient experienced PbtO2<5 for more than 1 hour the OR was 70 (CI 10-476).

Table 4: Association between PbtO2 parameters and DCI in univariate analysis

Parameter	*P*-value	OR	Confidence Interval
$PbtO2_{low}$<1.7mmHg	<0.0001	143	13-1526
PbtO2<5 for >1 hour	<0.0001	70	10-476
PbtO2<10 for >1 hour	<0.0001	54	6-477
$mPbtO2_{24}$<16.5mmHg	<0.0001	22.5	5-107
Time-Hypoxia product>20	<0.0001	45	8-260

P-values, Odd's ratios (OR), confidence intervals for PbtO2 parameters. Odds ratios are reported as the Odds of developing DCI.

Multiple Logistic Regression Analysis

Physiological and clinical variables found to have a relationship with DCI in univariate analysis were entered into multivariate models. Different PbtO2 parameters were examined in separate multivariate models. Only GCS, pupil reactivity and PbtO2 parameters remained in the final model. PbtO2 parameters were the only consistent statistically significant independent factors associated with DCI in multivariate logistic regression analysis and each PbtO2 parameter remained significant in multivariate analysis (PbtO2<5, p=0.032; PbtO2<10, p=0.018; $PbtO2_{low}$, p=0.029; and Time-Hypoxia product, p=0.026). GCS also was an independent variable associated with DCI when tested against

PbtO2<10 (p=0.028) and $mPbtO2_{24}$ (p=0.019), but not when tested against PbtO2<5 (p=0.104). When PbtO2 was <5mmHg on more than one occasion patients were almost 27 times more likely to have DCI (OR 26.9, p=0.002, 95% CI 3.5-206) than those with one or no episodes when controlled for GCS (OR 9.2, p=0.11, CI 0.6-143) and pupil reactivity (OR 4, p=0.240, CI 0.4-41). ICP and CPP parameters did not have an association with DCI. There was only a trend to significance with pupil reactivity (p=0.06) when tested with PbtO2<10. GCS was associated with DCI when tested with PbtO2<10 (p=0.015) and mPbtO224 (p=0.019) but not when tested against PbtO2<5 (p=0.110).Table 5 shows results for PbtO2<5 in a multivariate model with GCS and pupil reactivity.

Table 5: Multivariate model testing for associations of PbtO2<5, GCS and pupils with DCI

Parameter	*P*-value	Adjusted OR	C-I
PbtO2 < 5 for >1 hour	0.002	26.9	3.5-206
GCS ≤ 5	0.110	9.3	0.6-143
Pupils > 2	0.240	4.0	0.4-41

P-values, adjusted Odd's ratios (OR) and 95% confidence intervals (CI) for PbtO2<5, GCS≤5 and pupil reactivity>2

Discussion

This study examined associations between clinical and physiological factors, and in particular PbtO2, and DCI in 57 selected children with acute neurological injury managed in an ICU. The main findings were: 1) Low PbtO2 is an independent factor associated with DCI in children with severe neurological injury, 2) PbtO2 was significantly less, and reduced for a longer duration of time, in patients with DCI than those without, 3) DCI is very unlikely if PbtO2 is always >10mmHg which is consistent with similar thresholds associated with clinical outcome after TBI [384], and with critical reductions in CBF [147,

[312], and 4) when PbtO2 was < 5mmHg for more than 1 hour the risk of DCI was very high (OR 27, 95% CI 3.5-206).

Methodological Limitations

There are several potential limitations to this study. First, this is a single center study and requires repeat at another centre for external validity. Second, the number of patients who developed DCI was small. Third, compromised PbtO2 or elevated ICP was treated during this study. This may bias the results. It also remains unclear whether treatment of low PbtO2 can reduce the incidence of brain ischaemia/ hypoxia or DCI. If so, it is not known which intervention is best suited to prevent DCI. Third, patients may have developed ischaemia in areas remote from the PbtO2 monitor that did not progress to CT-diagnosed DCI; i.e. these data do not provide an estimation of the true incidence of cerebral ischaemia. Fourth, CT was used to diagnose cerebral infarction. Diffusion-weighted magnetic resonance images have a greater sensitivity for infarction. Therefore, the true incidence of DCI may be underestimated. However, CT scanning is the usual modality for follow-up imaging in neurocritical care and is the most frequently used imaging modality used in reports that describe DCI after head injury and meningitis [61, 220, 239, 287, 318, 340, 359]. Fifth, not all patients who had a PbtO2 monitor were included in the study because of the exclusion criteria. Importantly, patients who did not have follow-up imaging at least one week after admission were excluded. All of these patients survived their injury, however, and none developed delayed neurological deficit. Sixth, patients who underwent PbtO2 monitoring, particularly those with meningitis, were selected because of their presumed high risk; therefore this may bias our results toward a higher incidence of infarction in this population. Finally, the PbtO2 data does not contain enough detail to allow a more specific conclusion of what duration below individual PbtO2 thresholds may be tolerated. Also, these results cannot define the reasons why some patients who experience low PbtO2 proceed to infarction and some do not. This may relate to the duration of the insult, the underlying level of the metabolic activity of the tissue or intervention for compromised PbtO2. Despite these limitations, these data confirm a strong relationship between low PbtO2 and DCI.

Delayed Cerebral Infarction and Specific Pathology

The vast majority of children in this study had TBI. The exact incidence of delayed brain ischaemia after TBI, and in particular in children, is not fully elucidated in large part because of methodological variations or limitations in various studies; therefore the reports in the literature are conflicting. Some PET studies after TBI report a very low prevalence of ischaemia using global measures [401]. However, PET scans are generally performed on more stable patients and the investigation is temporally limited. Data from clinical studies using PbtO2, jugular venous saturation, Xenon-CT, regional measures of PET, and post-mortem studies [36, 75, 128, 351] suggest a much higher incidence of delayed ischaemia, particularly in more severely injured patients.

PTCI in adults is known to be associated with poor outcome, but the incidence and impact of PTCI in the paediatric population is not known. Marino et al [220] reported PTCI in 19% of adults after head injury. PTCI was the only independent predictor of outcome at 6 months. However, they included patients with moderate TBI and excluded patients who were in the ICU for less than 48 hours. Tawil et al [359] reported a PTCI incidence of 8% in patients with severe TBI but also excluded all patients who died within the first 24 hours of admission and those with diffuse cerebral infarction due to hypoperfusion. Therefore, this incidence may depend on which patients were evaluated and how the diagnosis of PTCI was made. The incidence of PTCI in this study was 13% in children with severe TBI. This study differed from the above reports in adult TBI in that it only considered patients with *severe* TBI and included patients who died within the first 24 hours and who had diffuse infarction due to hypoperfusion. It is important to establish the incidence of PTCI in a paediatric population since paediatric TBI differs from adult TBI in several important ways. For example, initial hypotension may have a stronger effect on adverse outcomes in children than in adults [273], the immature brain may be particularly vulnerable to ischaemia-hypoxia [287, 413], and unique to the paediatric population is NAI, which is known to have a particularly high incidence of infarction [287]. However, this study represents patients who had a PbtO2 monitor and intervention for low PbtO2; therefore the results may not necessarily be applicable to all children with severe TBI who are not monitored.

Six of the patients in this study had meningitis. In the paediatric population, infarction after meningitis may occur in 8%-27% [61, 340]; the exact incidence depending on the cause of the infection and clinical severity. In particular, hydrocephalus appears to increase the incidence of infarction in children with meningitis [61, 340]. Our patients with hydrocephalus each had a ventricular catheter to drain CSF and ICP was normalised in all. Infarction was likely frequent because 5 of the 6 patients had TBM, where cerebral infarction is particularly common due to the thick granulomatous exudate that accumulates in the basal cisterns around the arteries of the circle of Willis [112, 317]. In these patients cerebral ischaemia may occur despite normal ICP and treatment with antituberculous drugs and steroids [113].

PbtO2 Monitors

Although PbtO2 is a measure of local oxygen tension, it appears to provide a continuous measure of global brain oxygen particular when it is placed in normal-appearing white matter (Chapter 6). However, what the PbtO2 monitor value best approximates needs better definition. Nevertheless, it appears that the information can be used to limit secondary brain injury. Several therapies including aggressive ICP treatment, elevation of CPP, blood transfusion, and normobaric hyperoxia have been proposed to treat brain ischaemia-hypoxia [76, 168, 194, 263, 301, 338, 349, 373]. These interventions may be effective in treating low PbtO2 in individual patients with critical brain injury; however, there are potential adverse effects of each. A PbtO2 monitor, or any other monitor of brain physiology, may permit better targeted treatment of brain-injured patients and so may avoid potential deleterious side-effects of therapies applied to all patients, and focus on those patients most likely to benefit from a specific intervention.

Conclusion

This study found that low PbtO2, in particular when of a long duration, is an independent factor associated with DCI in children with acute neurological pathology. Conventional measures of brain physiology (ICP and CPP), however, did not always predict DCI. Early detection of low PbtO2,

therefore, may afford clinicians the opportunity for early intervention to prevent brain hypoxic-ischaemic injury in neuro-critical care and specifically, in children with severe brain injury.

Chapter 13

Does Adherence to Treatment Targets in Children with Severe TBI Avoid Brain Hypoxia?

Introduction

Critical care units that treat brain-injured children often may not have access to advanced neuromonitoring and infer the adequacy of brain oxygenation from targets recommended for ICP, CPP, Hb and PaO2. However, each of these targets continues to be debated [3, 8, 39, 193, 236, 260, 294]. These targeted parameters do not necessarily account for local and regional factors which may influence cellular function, such as changes in local oxygen and glucose delivery, cerebral vasoreactivity [269, 327], flow-metabolism mismatch [74] and increased tissue diffusion barriers [235].

Optimal CPP after TBI remains poorly defined. Higher CPP has been advocated to prevent secondary cerebral ischaemic episodes [300], but may increase systemic adverse effects [294]. A strong association between secondary insults and poor outcome is well documented in paediatric TBI studies [54, 56, 66, 71, 98, 170, 180, 273], yet there is little consensus on optimal CPP targets for children, or even the definition of hypotension [3, 8, 136, 299]. The relationship between CPP and metabolism may be disturbed by many factors [74, 368]. Conventional CPP treatment targets, therefore, may not prevent cerebral ischaemia in all patients whereas targeting supranormal CPP routinely may exacerbate vasogenic edema and increase the risk of acute respiratory distress syndrome [102, 294]. PbtO2 monitoring may help address some of these issues and allow CPP to be tailored to the specific injury and child. This study evaluates PbtO2 monitoring in children with severe TBI to determine whether achievement of

commonly accepted systemic and intracranial physiological treatment targets avoids brain tissue hypoxia.

Methods and Materials

Patient Selection

Data were collected prospectively from consecutive patients who underwent PbtO2 and ICP monitoring for brain injury over a 9-month period at Red Cross Children's Hospital from June 2006 to February 2007.

Analysis of Low PbtO2

Patient physiologic data were analysed to 1) identify the incidence of low PbtO2 and 2) examine the association between outcome and PbtO2. The incidence of low PbtO2 was calculated for the entire duration of monitoring and for the time periods when conventional targets to maintain ICP, CPP, Hb, PaO2 and pulse oximetry were met. For this "target" analysis data were excluded when time-linked parameters of ICP > 20mmHg, CPP < 50mmHg (this included episodes of systolic BP less than the fifth percentile for age or clinical signs of shock [3, 136]), Hb <8g/dl and PaO2 < 60mmHg or pulse oximetry < 90% were present. This allowed examination of PbtO2 levels when ICP, CPP, Hb and PaO2 were consistent with accepted thresholds.

Results

Patient Clinical and Radiographic Characteristics

In the study period 26 patients with severe TBI underwent PbtO2 monitoring. Mean age was 6.8 ± 3.4 years. Demographic and clinical characteristics are summarised in Table 1.

Table 1: Demographic and clinical characteristics on admission for 26 TBI patients for examination with PbtO2 and treatment targets

Characteristic	Data
Age	6.8 ± 3.4 (9 months-14 years)
Gender: Male/Female	22/4
Mechanism of injury	
MVA pedestrian	17
MVA passenger	4
Blunt assault	2
Gunshot wound to the head	2
Crush injury	1
Postresuscitation GCS	
GCS 3	1
GCS 4	6
GCS 5	8
GCS 6	5
GCS 7	4
GCS 8	2

Median GCS	5
GCS motor score	3 ± 1 (1-5)
Pupillary abnormalities	
Unilateral non-reactive	2
Bilateral non-reactive	3
Polytrauma	13
Time to start of monitoring	13 ± 15.4 hrs post-trauma
Initial Hb	10 ± 1.66 g/dl
Initial MAP	78 ± 16
Length of ICU stay	8 ± 4.2 days
Length of follow-up	7.4 months (3-13)
Initial CT features	
Diffuse Injury I	3
Diffuse Injury II	12
Diffuse Injury III	6
Diffuse Injury IV	3
Evacuated mass lesion	2 (1 EDH, 1 SDH)
Non-evacuated mass lesion	0

Where applicable, data are presented as means ± standard deviation, except where stated otherwise. **EDH,** extradural hematoma; **SDH**, subdural hematoma.

Monitoring and Physiological Variables

ICP and PbtO2 monitoring was started within 12 hours of injury in 17 patients and between 12 and 24 hours in 7 patients. Monitoring was started after 24 hours in 2 patients who were transferred from other units. Both these patients had normal (Marshall I) admission CT scans. The average time to start of monitoring after injury was 13 ± 15.4 hours. The mean duration of intracranial monitoring was 123.7 ± 67.1 hours. Mean ICP and CPP during the period of monitoring were 15 ± 8 mmHg and 68 ± 15 mmHg respectively. Mean maximum ICP and mean minimum CPP were 35 ± 19 mmHg and 40 ± 16 mmHg respectively.

PbtO2 Data Summary

PbtO2 data from 3217 hours were analysed. When patients had 2 PbtO2 monitors *in situ*, the lower reading of the 2 catheters was used to calculate the incidence of low PbtO2. For all patients, mean PbtO2 during the period of monitoring was 35 ± 15 mmHg. Mean minimum and maximum PbtO2 were 10 ± 6.5 mmHg and 67 ± 19 mmHg respectively. At least one episode of compromised PbtO2 (<20mmHg) occurred in 24 patients.

PbtO2 and Treatment Targets

Brain oxygen values less 20 mmHg, 15 mmHg, 10 mmHg or 5 mmHg for the entire monitoring period and for the time periods where defined management targets (ICP, CPP, Hb, SaO2) were met are displayed in Tables 2 and 3 respectively. For the defined management target analysis, 11% of data were excluded because at least one parameter required for this analysis was missing, and 23.5% were excluded because the defined targets were not achieved. This left 2107 hours for evaluation, in which all targets were achieved: ICP was < 20mmHg, CPP ≥ 50 mmHg, PaO2 ≥ 60 mmHg, SaO2 ≥ 90%, and Hb ≥ 8g/dl. Despite the achieved management targets, 80% of patients had one or more episodes of PbtO2 less than 20 mmHg, 56% had episodes less than 15 mmHg, 32% had episodes

less than 10 mmHg, and 12% had episodes less than 5 mmHg (Table 3). Only 20% of patients had no episodes of PbtO2 < 20mmHg during the time that management targets were achieved.

Table 2: Low PbtO2 episodes for total duration of monitoring in 26 patients (3217 hours)

PbtO2 value	No. of patients	Duration (hours)
<20 mmHg	24 (92%)	7 (4.3-15.8)
<15 mmHg	18 (69%)	4.5 (2.8-10.3)
<10 mmHg	15 (58%)	1 (1-5)
<5 mmHg	6 (23%)	5 (1.8-6.8)

Table 2: No. of patients, number of patients experiencing one or more episodes of PbtO2 less than the respective thresholds. **Duration**, cumulative duration of ischaemic/hypoxic episodes calculated as an average from the number of patients with PbtO2 values below the corresponding threshold and expressed as median (interquartile range) in hours.

Table 3: Low PbtO2 episodes for time periods where all treatment targets were achieved. 25 patients* (2107 hours).

PbtO2 value	No. of patients	Duration (hours)
<20 mmHg	20 (80%)	5.5 (2-11.5)
<15 mmHg	14 (56%)	2 (1-6)
<10 mmHg	8 (32%)	1.5 (1-2)
<5 mmHg	3 (12%)	1 (1-1.5)

Table 3: No. of patients, number of patients experiencing one or more episodes of PbtO2 below the respective thresholds. **Duration**, cumulative duration of ischaemic/hypoxic episodes calculated as an average from the number of patients with PbtO2 values below the corresponding threshold and expressed as median (interquartile range) in hours. * For one patient treatment targets were not met at any point during the complete dataset (this patient died within 24 hours of injury).

Discussion

This study examined 26 children with severe TBI who underwent continuous PbtO2 monitoring during their ICU care. Each child was managed according to published management guidelines for paediatric TBI [4]. These and other guidelines emphasize control of ICP, CPP, oxygenation and Hb among other variables while the child receives ICU care. The important finding from this study is that, despite achieving these management targets, compromised PbtO2 was common and about one third of patients had evidence of significant brain hypoxia (PbtO2 < 10mmHg).

Methodological Limitations

There are several potential limitations to this study. First, the study is not a pure observational study in that efforts to correct compromised PbtO2 were made. This may bias the results. Second, the sample size is small which means these results are preliminary. Nevertheless, the data are persuasive in that one-third of patients who had met treatment targets for ICP, CPP, oxygenation and Hb still had severe brain hypoxia (PbtO2 < 10mmHg). Third, the age range of children included in our analysis is large. The children in this study were all less than 15 years old, however. Therefore, the data reliably reflect PbtO2 monitoring in a paediatric population. This is important since the physiology of older adolescents may be more similar to that of adults than that of younger children. There are also very few patients less than one year of age. This is important since these patients may have different physiological characteristics to that of older children. Because the sample size is small, however, age-specific levels of PbtO2 could not be examined. Fourth, the mean time to start of PbtO2 monitoring was relatively late. With earlier start times, however, more episodes of brain hypoxia might have been observed. Fifth, the patients included in this study represent the first patients who had PbtO2 monitoring at our institution. There is a learning curve associated with using a new technology and how to respond to the information it provides. Despite these limitations these findings are consistent with those observed in adult TBI in the early period after resuscitation [351] and in particular suggest that guidelines that describe optimal management after TBI in children may need further study.

Current Guidelines for Childhood TBI Treatment

The recently published guidelines have summarized the current literature on paediatric TBI care [4] and highlight the paucity of data available to support evidence-based protocols for the management of paediatric severe TBI. Consequently, specific thresholds to treat ICP, CPP, Hb and systemic oxygenation, the foundation of TBI care, are not clearly established in children. In addition, most clinical studies that address paediatric TBI include few patients and so age-related differences in physiologic variables often are indiscernible. In the published guidelines, treatment of ICP ≥ 20mmHg

was recommended as an option, and a guideline for avoiding CPP <40mmHg (and aiming for CPP ≥50mmHg as an option) was recommended [7, 8]. Hypotension during resuscitation was defined as SBP below the fifth percentile for age or signs of decreased perfusion, and hypoxia was defined as PaO2 <60-65mmHg or SO2 < 90% [3]. Although the definition of systemic hypoxia is largely accepted [3, 273], recent studies showing increased PbtO2 and improved cerebral metabolism with normobaric hyperoxia in head-injured adults have stirred debate about what constitutes optimal oxygenation in TBI [236, 263, 290, 373]. Conservative thresholds for blood transfusion have been advocated in general critical care patients, with recent trends favoring transfusing at a Hb trigger of 7g/dl [183, 288]. The appropriateness of these criteria for brain-injured patients is uncertain, though, and higher Hb has been associated with variable increases in PbtO2 in head-injured adults [194, 338]. A less restrictive threshold was selected for analysis in this present study because TBI patients may be at greater risk for cerebral ischaemia and the optimal Hb may be higher for this group of patients. The treatment targets chosen for analysis in this series; therefore, were based on reasonable thresholds for these parameters from the current literature although there is insufficient data to support a standard for each [3, 7, 8].

Incidence of Compromised PbtO2

These results demonstrate that low PbtO2 was surprisingly common despite what appears to be adequate resuscitation and critical care management according to current paediatric TBI guidelines. Only 20% of patients with optimised parameters did not experience any episodes of PbtO2 < 20 mmHg even though treatment targets were met. In fact, almost one third had one or more episodes of PbtO2 < 10mmHg. This is consistent with observations in adults during the early hours of resuscitation after TBI [351]. These data also support the results of PET studies which showed significant ischaemia in early head injury despite adequate CPP and ICP control [74], and post-mortem brain examinations [128]. However, whether treating low PbtO2 benefits the paediatric patient with severe TBI still needs to be determined.

Conclusion

On the basis of these and other data that show a high incidence of possible brain ischaemia/hypoxia despite apparently adequate treatment (by reference to current guidelines) it appears reasonable to argue that other measures of brain physiology or metabolism are needed in an attempt to optimise treatment of children with severe TBI. What also will need study is whether correction of compromised PbtO2, or perturbations in any of the other modalities used, has any deleterious effects.

Chapter 14

Acute Clinical Grading in Paediatric Severe TBI and its Association with Subsequent Secondary Insults

Introduction

In paediatric trauma patients admission clinical assessment and clinical grading can be used to guide treatment protocols and to predict outcome [50]. In large part, these various grading systems, e.g. the GCS [362], Paediatric Trauma Score [365, 365], Paediatric Index of Mortality [337], pupillary reactivity [390] and brain CT classification [223] are associated with the severity of the patient's primary injury. However, outcome after severe TBI is affected also by secondary cerebral injury that evolves during the days after the initial primary insult. Common secondary cerebral insults in TBI that are associated with adverse outcomes include elevated ICP, reduced CPP, hypotension, systemic hypoxia, and brain hypoxia [17, 57, 119, 308, 334]. These and other secondary insults, while potentially avoidable, are common and may contribute to death in as much as 42% of children who die after admission for head injury [328]. The relationship between outcome and the various grading or scoring systems used to classify paediatric trauma patients is well described. However, the relationship between these grading systems of injury and the likelihood of secondary insults is less well-defined.

This study examines the relationship between acute measures of injury severity on admission and the subsequent development of secondary cerebral insults after ICU admission in children with severe TBI.

Methods and Materials

Patient selection

Clinical and physiologic data were obtained as previously described (chapter 8). Patients were included in this study if: 1) they underwent continuous ICP, CPP and PbtO2 monitoring and 2) initial injury was classified according to the GCS, motor component of the GCS, Paediatric Trauma Score (PTS), Paediatric Index of Mortality (PIM 2), pupil reactivity, and the Marshall CT classification of head injury. Each of these grades had to be recorded for an individual patient to be included in the study. The details of these grading systems are given I Chapter 8. Age also was used in this study to classify patient risk since age may influence outcome.

Physiological Monitoring

Abnormal values (Chapter 8) for PbtO2, ICP, CPP, PaO2 and SaO2 were examined for association with each of the above clinical grading scores. Treatment factors were also analysed similarly.

Data and Statistical Analysis

The individual acute clinical scores and head CT classification recorded in each patient were evaluated as independent variables and subsequent physiological parameters as dependent variables. Spearman correlation coefficients were used to determine relationships between scores and physiological variables. For categorical scores, the Pearson's chi-square was used for relations with categorical variables and Kruskal-Wallis for continuous variables. The Kruskal–Wallis test evaluates equivalence between 2 medians while ignoring the ordering in the categorical covariates. The Pearson chi-square was used to test the frequency distribution of categories within the individual scores. Scores that were significant in univariate analysis were entered into a multivariate analysis

model. Significance was set at p=0.05. Data are reported as means ± SD or medians (interquartile range and/or range).

Results

Clinical Characteristics

Fifty-two paediatric patients with severe TBI who were monitored for ICP, CPP and PbtO2 between June 2006 and May 2008 were included in the study. Clinical, demographic, physiological and treatment variables for these patients have been summarised previously in Chapter 10.

Univariate Analysis

GCS: Postresuscitation GCS was significantly associated with lowest CPP (p=0.004), CPP<40 (p=0.017), CPP<50 (p=0.019), PbtO2<5 (p=0.008) [Fig.1], and PbtO2<10 (p=0.045). There were no associations with any other physiological or treatment variables, including the indices of elevated ICP.

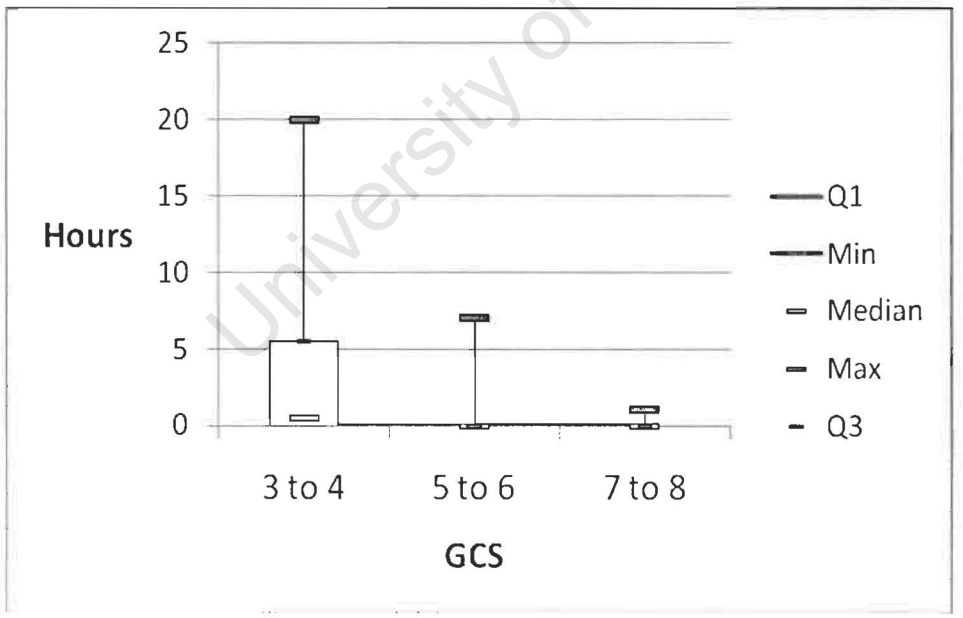

Figure 1: Box-and-Whisker plot for initial GCS and episodes of PbtO2<5mmHg. GCS is grouped in 3 categories: 3-4 (n=14), 5-6 (n=22) and 7-8 (n=16), with the respective frequencies of episodes of PbtO2<5mmHg shown for each.

Motor component of the GCS: The motor response of the GCS had no significant relation with any variables when using with the Spearman's correlation coefficient. However, when the data were examined using the Kruskal-Wallis test a marginal relationship with PbtO2<5 (p=0.046) and PbtO2<10 (p=0.047) was observed.

PIM 2: The PIM 2 score was associated with CPP<40 (p=0.008), mICP>20 (p=0.0013) and ICP_{peak} (p<0.0001).

PTS: The PTS had a weak relationship with PbtO2<10 (p=0.046), but not with any other variables.

Pupil reactivity on admission: Pupil reactivity was associated with lowest CPP (p=0.003), CPP<40 (p=0.024), CPP<50 (p=0.032), PbtO2<5 (p=0.026), and PbtO2<10 (p=0.031).

CT classification: Individual categories according to admission head CT scan findings demonstrated relationships with mICP>20 (p=0.017), and lowest CPP (p=0.006), PaO2<60 (p=0.029) and SaO2<90% (p=0.023). DCH also was associated with individual Marshall categories (p=0.008). When the various CT categories were dichotomised to grade I+II and grade III+IV, the following associations were observed: $mICP_{24}$, (p=0.027), lowest CPP (p=0.003) [Fig.2], CPP<50 (p=0.015) and $mICP_{total}$ (p=0.046). The distribution of observations within the categories of the classification was significantly different: most patients demonstrated grade II and III changes on the initial head CT (44 of 52 patients).

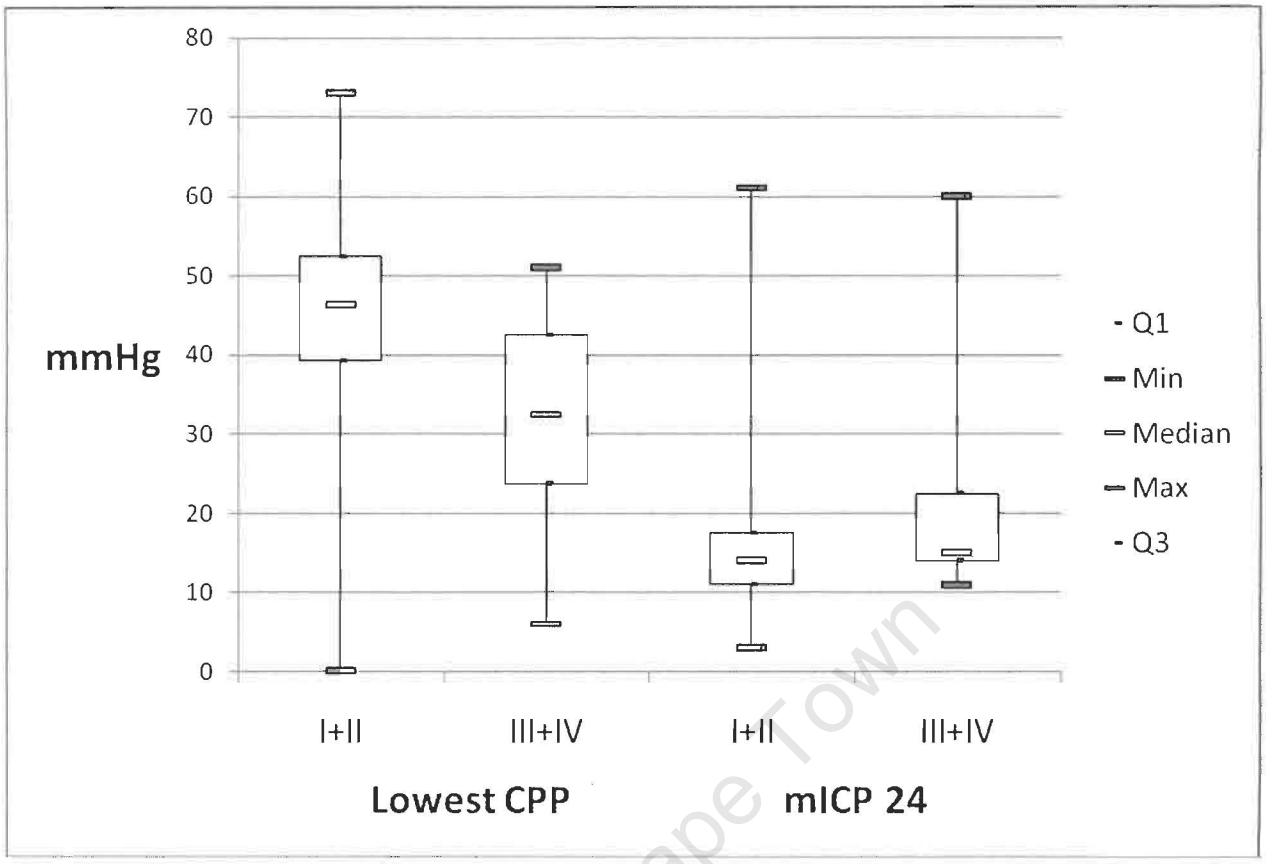

Figure 2: Box-and-Whisker plot CT classification with Lowest CPP and $mICP_{24}$. Relationship between CT classification (only diffuse injury I+II compared with III+IV, n=50) and lowest CPP and mean ICP for the first 24 hours ($mICP_{24}$). Evacuated mass lesion patients excluded (n=2).

Age: Age was significantly associated with: lowest CPP (p=0.007), CPP<40 (p=0.001), and CPP<50 (p=0.002) but with no other variables.

Treatment variables: Head CT classification was significantly associated with DCH (p=0.015) (more patients with Diffuse Injury 3 and 4 received DCH). Pupil reactivity demonstrated a trend towards a significant association with DCH (p=0.056) and thiopentone (p=0.073). No other scores demonstrated any other associations with treatment variables.

Multivariate Analysis

Variables found to be significantly associated with secondary cerebral insults were entered into multivariate analysis. These results are summarised in Table 1. The PIM 2 score was associated with mICP>20 (p=0.001), ICP_{peak} (p<0.0001), and CPP<40 (p=0.001). Initial GCS was associated with lowest CPP (p=0.016) and PbtO2<5 (p=0.017). Pupil reactivity was associated with lowest PbtO2 (p=0.039) and had a trend towards an association with lowest CPP (p=0.057), CPP<40 (p=0.073), PbtO2<5 (p=0.076), and PbtO2<10 (p=0.057). Age was associated with lowest CPP (p<0.0001), CPP<40 (p=0.004) and CPP<50 (p<0.0001). There were no scores that had significant associations with ICP>20, $mICP_{24}$, $mICP_{total}$, PaO2<60, lowest PaO2, and SaO2<90%. No significant associations between PTS, CT classification, or motor component of the GCS and any of the measured variables were found in multivariate analysis. There were no significant associations between scores and treatment variables in multivariate analysis.

Table 1: Multivariate Analysis of Clinical Grading and Secondary Physiological Derangements.

The associations between scores and physiological measures with significant relationships or trends are shown. Asterisks (*) denote significant results.

Physiological category	Predictive score (*p*-value) [95% C-I]
ICP	
ICP>20	None
mICP>20	PIM 2 (*p*=0.001) [12.5-46] *
ICPpeak	PIM 2 (*p*<0.0001) [22.9-64.7] *
mICP24	None
$mICP_{total}$	None
CPP	
Lowest CPP	Initial GCS (*p*=0.016) [0.7-6.5] *
	Age (*p*<0.0001) [0.8-3] *
	Pupils (*p*=0.057) [-11.2 to 0.2]
CPP<40	PIM 2 (*p*=0.001) [4.2-17.1] *
	Age (*p*=0.004) [-0.9 to -0.2] *
	Pupils (*p*=0.073) [-0.167 to 3.7]
CPP<50	Age (*p*<0.0001) [-3.7 to -1.1] *
Systemic hypoxia	
PaO2<60	None
Lowest PaO2	None
SaO2<90%	None

PbtO2	
Lowest PbtO2	Pupils (p=0.039) [-6.6 to -0.2] *
PbtO2<5	Initial GCS (p=0.017) [-1.8 to -0.2] *
	Pupils (p=0.076) [-0.2 to 3.4]
PbtO2<10	Pupils (p=0.057) [-0.2 to 10.3]

C-I, Confidence Interval

Discussion

Fifty-two children with severe TBI were studied to examine the relationship between acute scores of injury severity, including postresuscitation GCS, PIM 2, PTS, CT classification, pupil reactivity and age, and subsequent secondary cerebral insults, in particular elevated ICP, reduced CPP, compromised PbtO2 and systemic hypoxia. The main findings were that none of the scoring systems had a consistent relationship with all potential secondary insults, and the strength of the association with different measures of secondary cerebral insults differed between the different scores. These results suggest that while acute grading systems may help predict outcome they may not always predict whether a paediatric patient will develop secondary cerebral insults after severe TBI.

GCS: The relationship between postresuscitation GCS and outcome after TBI is well described (Chapter 2). Since sedation in the acute phase may influence two components of the GCS, (eye opening and verbal responses), the motor component of the GCS is often considered to represent a more reliable assessment. In a large series of paediatric severe TBI, Ducrocq et al [99] reported that a threshold GCS of 5 or less was associated with mortality and poor outcome. In our study, initial GCS demonstrated an association with different measures of CPP and PbtO2. However, GCS was not

associated with various measures of elevated ICP. Furthermore, the motor component of the GCS had no consistent relationships with secondary cerebral insults.

PTS: The PTS is a combined trauma and physiological score developed to predict outcome in paediatric trauma patients [365]. Its use has been reported in paediatric TBI [99, 130] and PTS<3 is associated with increased mortality [50, 130]. Although widely used in the assessment of paediatric trauma patients, in this study the PTS failed to correlate with any of the physiological variables known to be associated with secondary insults.

PIM 2: PIM 2 is evaluated on admission to the ICU. It is easier to use than PRISM III which has 17 variables and evaluates patients not on admission but during the first 24 hours in the ICU [276]. Although not specifically designed for the evaluation of trauma patients, PIM 2 has been reported to have a close relationship with outcome in paediatric head injury [130]. We observed that PIM 2 was associated with several indices of elevated ICP. However, we did not observe an association between PIM 2 and episodes of compromised PbtO2 or systemic hypoxia.

Pupils: Pupillary reaction is strongly associated with outcome after TBI [224, 390]. In this study, pupil reaction was associated with PbtO2 and CPP indices, but not with elevated ICP.

CT classification: There are several classification systems that attempt to relate the initial CT head scan findings to outcome [66, 99, 274, 367]. The most commonly used system is that developed by Marshall et al [223]. In this study we observed that the Marshall grade was associated with some indices of ICP, presumably reflecting the association of compressed cisterns and midline shift (diffuse injury III-IV) with ICP. Also, grade III and IV were associated with DCH in univariate analysis, which probably reflects both its association with elevated ICP and the tendency to perform DCH in the setting of obliterated cisterns and high ICP. However, we did not observe an association between the Marshall grade and PbtO2 indices, and with CPP<50 only in univariate analysis.

Age: In the present study age was related to all indices of CPP. This may reflect the lower physiological thresholds in younger children or the tendency to target higher CPP values with increasing age.

A number of physiological measures had no relationships with acute assessment scores (Table 1). There were also no predictors for treatment variables, except for CT classification with DCH (univariate analysis only).

Methodological Limitations

There are a number of possible limitations to this study. First, the sample size is relatively small. It is possible that with a larger sample more consistent relationships between the various scores and physiological variables may have been seen. However, the study was limited to only patients who received ICP, CPP and PbtO2 monitoring. Often only ICP and CPP or BP are evaluated as secondary insults, yet brain hypoxia may occur even when ICP and CPP are adequately managed or even normal (Chapter 13), so the addition of PbtO2 as an indicator of possible secondary injury can help detect episodes of secondary injury that may be otherwise undetected. Second, some but not all scores used to classify TBI patients were examined. For example, the following scores were not obtained: Injury Severity Score, Head Abbreviated Injury Severity Score, PRISM III, and Relative Head Injury Severity Score. Instead the scores chosen for the study are commonly used in paediatric trauma units and paediatric ICUs. Third, the secondary insults we evaluated did not include hypo- or hyperglycemia, pyrexia, seizures or sepsis. However, the secondary insults chosen for analysis have been extensively reported and each is known to be associated with adverse outcome after TBI. Fourth, it cannot be excluded that prompt identification and treatment of potential secondary insults did not confound these results. However, management of patients was not directed by patients' clinical scores. Similar treatment was delivered to all patients. Also, secondary insults in this series were frequent (Chapter 10); therefore, if there were significant associations between the high risk scores and the frequency of secondary insults, these would likely have been demonstrated in this cohort of patients.

Conclusion

Acute assessment scores that describe the primary injury sustained by children with severe TBI have a variable relationship with physiological markers of secondary cerebral injury after admission to the PICU. Although there were associations between individual scores and select measures of secondary cerebral insults, none of the scores evaluated reliably predicted each and every secondary insult. Based on these results, grading systems used to classify initial injury severity while they may guide initial treatment appear to have a limited value in predicting who is at risk for secondary cerebral insults. Therefore clinicians should remain vigilant for the development of secondary insults in all patients who present with significant head trauma.

Chapter 15

The Effect of ICP Reduction with Decompressive Craniectomy on PbtO2

Introduction

Although the general relationship between ICP and PbtO2 is variable when data from all patients are considered, elevated ICP may have significant effects on PbtO2 in individual patients. One such clinical situation that may reveal this relationship is elevated ICP requiring DCH. Because this is performed for ICP unresponsive to medical therapy, ICP is typically markedly elevated before DCH.

There has been renewed interest in DCH for the treatment of elevated ICP in TBI. Although many large studies have been reported in adults [48], there are few reports limited to children, and these reports are generally small studies [30, 110, 111, 171, 304, 360]. Changes in PbtO2 after DCH have only been described in adult patients [163, 291, 349].

This study examines the ICP and PbtO2 changes in children with diffuse traumatic brain swelling after DCH for elevated ICP refractory to medical management.

Methods and Materials

Data for consecutive patients less than 15 years old who underwent decompressive craniectomy for TBI at Red Cross Childrens Hospital between June 2006 and May 2008 were collected. Only craniectomy for diffuse swelling was considered; procedures where mass lesions were simultaneously removed were excluded. Data were extracted for ICP and PbtO2 before and after the procedure. All patients were treated for ICP and PbtO2 as previously described.

Statistical Analysis

Comparisons were made between values for ICP, MAP and PbtO2 for the 4 hour period before DCH, the 4 hour period after DCH and the 24 hour period after DCH. Only cases in which the PbtO2 catheter remained in the same location were analysed. PbtO2 data were excluded if a new PbtO2 catheter positioned during surgery. Data are presented as means ± standard deviation (SD) or median and IQR. Differences were defined as statistically significant if $p < 0.05$. The non-parametric Wilcoxon signed-rank test was used to compare pre- and post-intervention readings. Outcome was assessed with the GOS.

Results

Seven patients underwent DCH for diffuse swelling during this period. PbtO2 data from 1 patient were excluded from analysis because a new PbtO2 had been placed in a different location during the craniectomy. One other patient was not considered because DCH had been performed for removal of epidural and intracerebral haematomas. Therefore, ICP data for 7 patients and PbtO2 data for 6 patients were analysed. Mean age was 7 ± 4.6 years old. Median GCS before DCH was 5 (IQR 4 to 5.25). At the time of DCH, a unilateral unreactive pupil was documented in 2 patients and bilaterally unreactive pupils in 2. In all patients elevated ICP was refractory to conventional medical management before DCH. In 3 patients thiopentone was used before DCH.

ICP before and after DCH (n=7): Baseline ICP (average of 4 hours before craniectomy) was 42 ± 15mmHg compared with 14 ± 7mmHg immediately after DCH (first 4 hours, $p<0.0001$) and 15 ± 6mmHg for the 24 hour period after DCH ($p<0.0001$) (Table 1 and Figure 1). There was no significant difference between ICP in the 4 hours after craniectomy and the 24 hour period after DCH ($p=0.61$). No patients required thiopentone therapy after surgery.

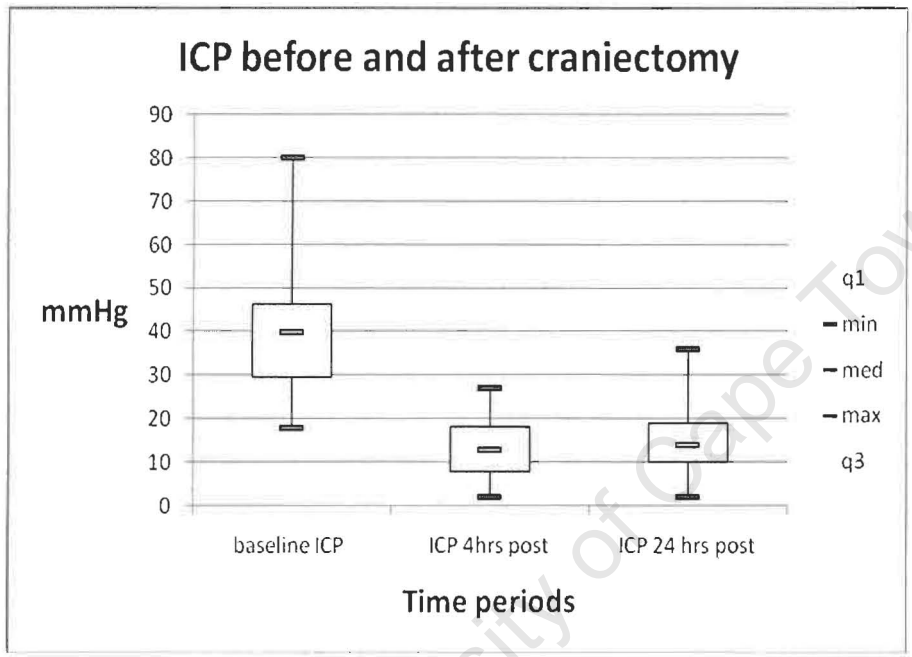

Figure 1: **Box-and-Whisker plot demonstrating ICP before and after DCH.** ICP values for (as medians, interquartile range [q1, q3], minimum and maximum) for 4 hours before craniectomy (first column: Baseline ICP) compared with ICP immediately after craniectomy (second column: ICP 4 hrs post) and over the 24 hour period after DCH (third column: ICP 24 hrs post). N=7 patients.

PbtO2 before and after DCH (n=6): Episodes of PbtO2 < 10mmHg occurred in 4 of these patients in the 4 hours before DCH. For each of these 4 patients mean PbtO2 before craniectomy was < 20mmHg (mean for 4 patients, 11 ± 7mmHg). In 2 patients mean PbtO2 before DCH was >20mmHg (23±4mmHg and 39 ± 2mmHg). For all 6 patients, mean baseline PbtO2 was 18.7 ± 12.8mmHg compared with 33.3 ± 17mmHg ($p=0.038$) in the first 4 hours after DCH and 42.8 ± 15.4mmHg

(p=0.027) for the whole 24 hour postoperative period (Table 1 and Figure 2). For the 2 patients whose mean baseline PbtO2 was >20mmHg, PbtO2 in the first 4 hours after surgery was slightly lower (25±11mmHg) than at baseline (31 ± 9mmHg) but then recovered to values slightly higher than baseline (37 ± 18mmHg in the 24 hour postoperative period). When only patients with low PbtO2 before surgery were considered (n=4), baseline PbtO2 was 11±7mmHg compared with 37.7±19mmHg for 4 hours after DCH and 45.7±13 for 24 hours after DCH (p<0.0001). MAP before surgery was 91 ± 13 mmHg and 78 ± 11 mmHg for the 24 hour period after craniectomy. Corresponding FiO2 was 73 ± 21 and 48 ± 6.

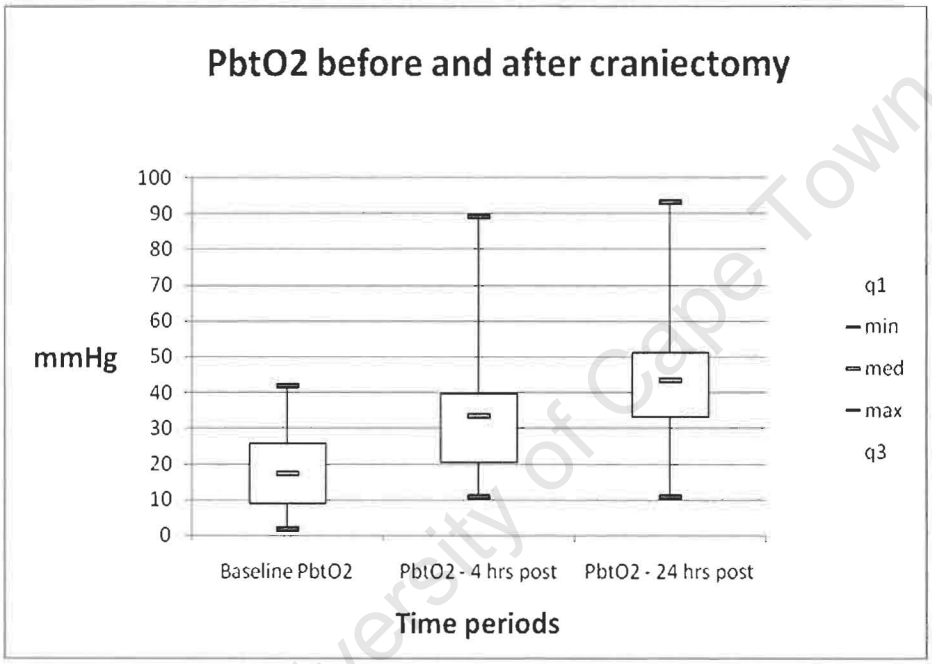

Figure 2: **Box-and-whisker plot demonstrating PbtO2 before and after DCH.** PbtO2 values (as medians, interquartile range (q1, q3), minimum and maximum) for 4 hours before craniectomy (first column: Baseline PbtO2) compared with PbtO2 immediately after craniectomy (second column: PbtO2 4 hours post) and over the 24 hour period after craniectomy (third column: PbtO2 – 24 hrs post). N=6 patients.

Table 1: ICP and PbtO2 data for 4 hours before, 4 hours after DCH and 24 hours after DCH

	Baseline	4 hours after	24 hours after	*p*-value
ICP (7 patients)	42 ± 15	14 ± 7*	15 ± 6†	<0.0001* /<0.0001†
PbtO2 (6 patients)	18.7±12.8	33.3±17*	42.8±15†	0.038* / 0.027†

Data are presented as means ± standard deviation.

Clinical Outcome

Mean time of follow-up was 12 ± 5 months (range 6-21). Outcome was favourable in 4 (57%) and unfavourable in 3 (43%) patients. There were no vegetative survivors and no deaths; all survivors were discharged home. One patient had a ventriculoperitoneal shunt placed for hydrocephalus.

Case Illustration

This 5-year old boy was a pedestrian involved in a MVA in which he sustained an isolated head injury. He was intubated at the scene, following which he was brought to the emergency room of the hospital where 1.5 hours after injury his post-resuscitation GCS was 4T/15 (abnormal flexion motor response). His postresuscitation BP was 110/63 and his Hb was 10.1 g/dl. He had no other injuries apart from lung aspiration; his PaO2/ FiO2 ratio was 19 kPa/ 0.3. Head CT revealed features of a diffuse axonal injury with some effacement of the basal cisterns (Fig 3 a+b). PbtO2 and ICP catheters were placed in the left frontal lobe for monitoring in the paediatric ICU. Head CT obtained after the monitors were placed confirmed that the catheters were optimally located and not in an area of hypodensity.

Moderate ICP elevation up to 25mmHg in the initial period was treated adequately with medical measures, including analgesia (morphine), sedation (Midazolam, Lorazepam), and hypertonic saline (5% solution). Initial PbtO2 readings were within an acceptable range (greater than 20 mmHg). At 20

hours post-injury however, ICP progressively increased despite medical treatment including increased sedation, mannitol, hypertonic saline, and BP optimisation. Barbiturate therapy was not commenced due to the labile nature of his BP. PbtO2 readings remained stable during the early phase of ICP elevation but decreased steadily thereafter. Since he had failed medical treatment of increased ICP and there was progressive PbtO2-compromise, the patient was taken to the operating room for a DCH 24 hours after his injury and 3 hours after his ICP first increased. The course of ICP and PbtO2 readings before surgery is shown in Fig 4.

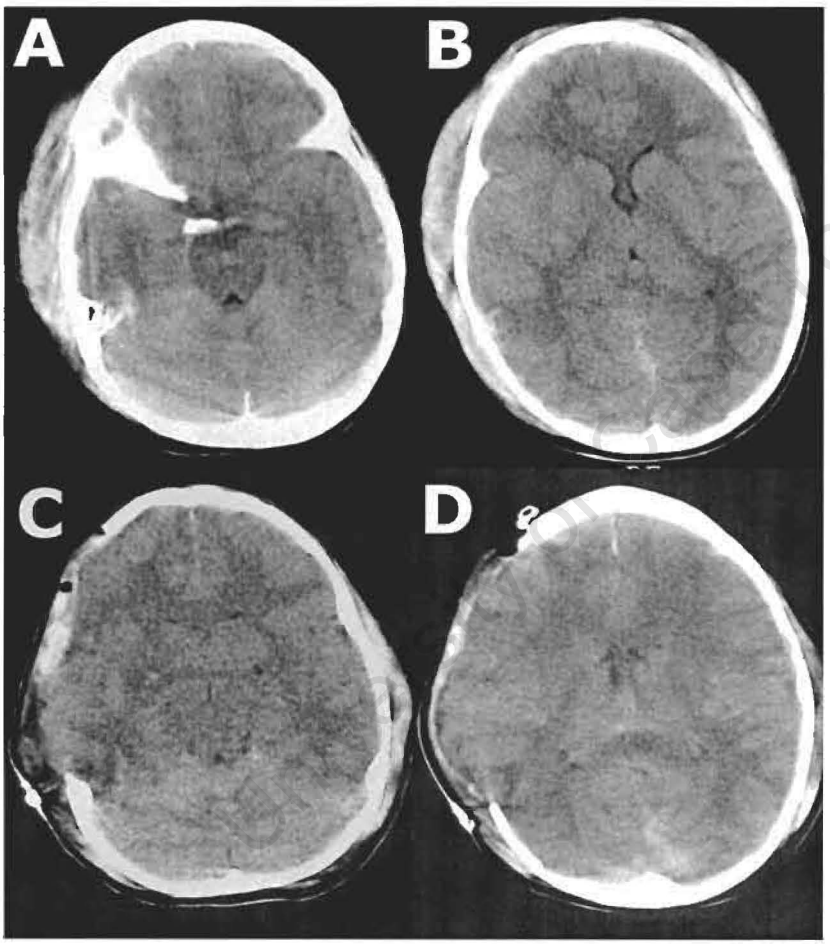

Figure 3: a+b, CT head of the patient before surgery; **c+d**, CT head of the patient after DCH.

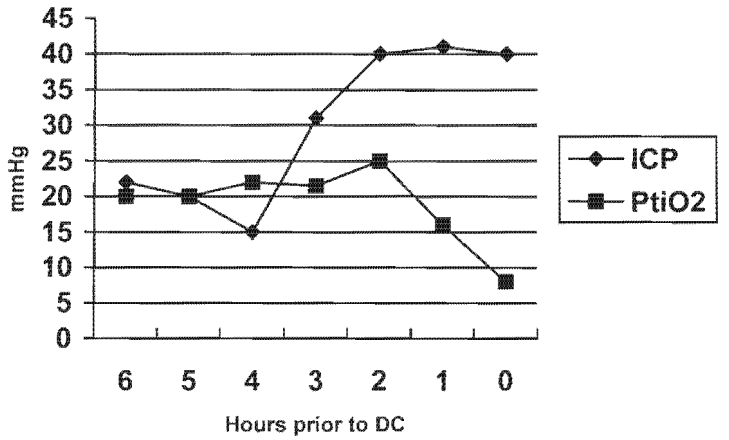

Figure 4: Graph demonstrating ICP elevation and PbtO2 deterioration before surgery.

Intraoperative Course

A right-sided DCH was performed; ICP and PbtO2 recordings from the contralateral hemisphere during the procedure were thus available. In the operating room immediately before surgery, ICP was 45 mmHg and PbtO2 was 8mmHg with an FiO2 of 60% giving a PaO2/ FiO2 of 31 kPa/ 0.6. His PaCO2, BP and Hb were 4.1 kPa, 120/ 85 and 12.2 g/dl respectively. The FiO2 (100%) and MAP (105mmHg) were increased. However, this only increased the PbtO2 to 16 mmHg (i.e. still compromised PbtO2). When the bone flap was removed the PbtO2 increased over the next 3-4 minutes to 26 mmHg. On widely opening the dura, PbtO2 further increased to 34 mmHg. The dura was closed using a large pericranial graft for augmentation. At the end of the craniectomy (skin closure), ICP was 8 mmHg and PbtO2 was 30mmHg. The patients MAP was 67 and PaO2 (using a FiO2 of 40%) was 26mmHg. The intraoperative PbtO2 data is shown in Fig 5.

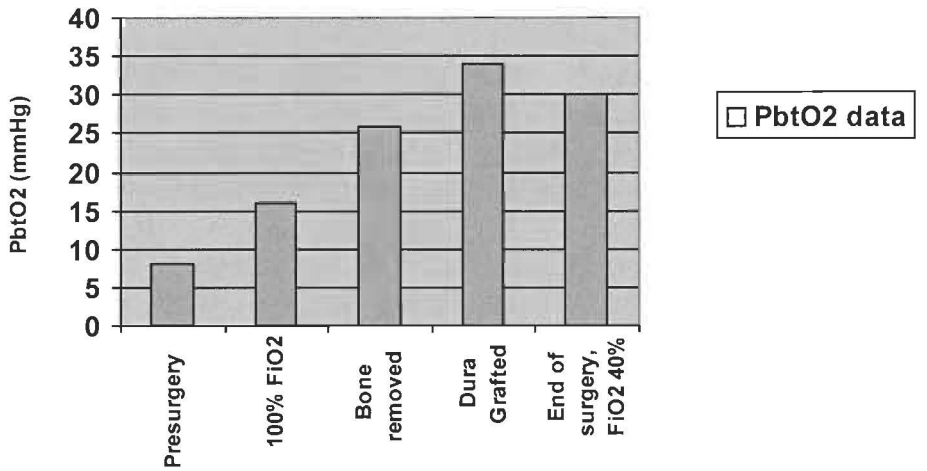

Figure 5: Graph showing the time course of PbtO2 changes during surgery

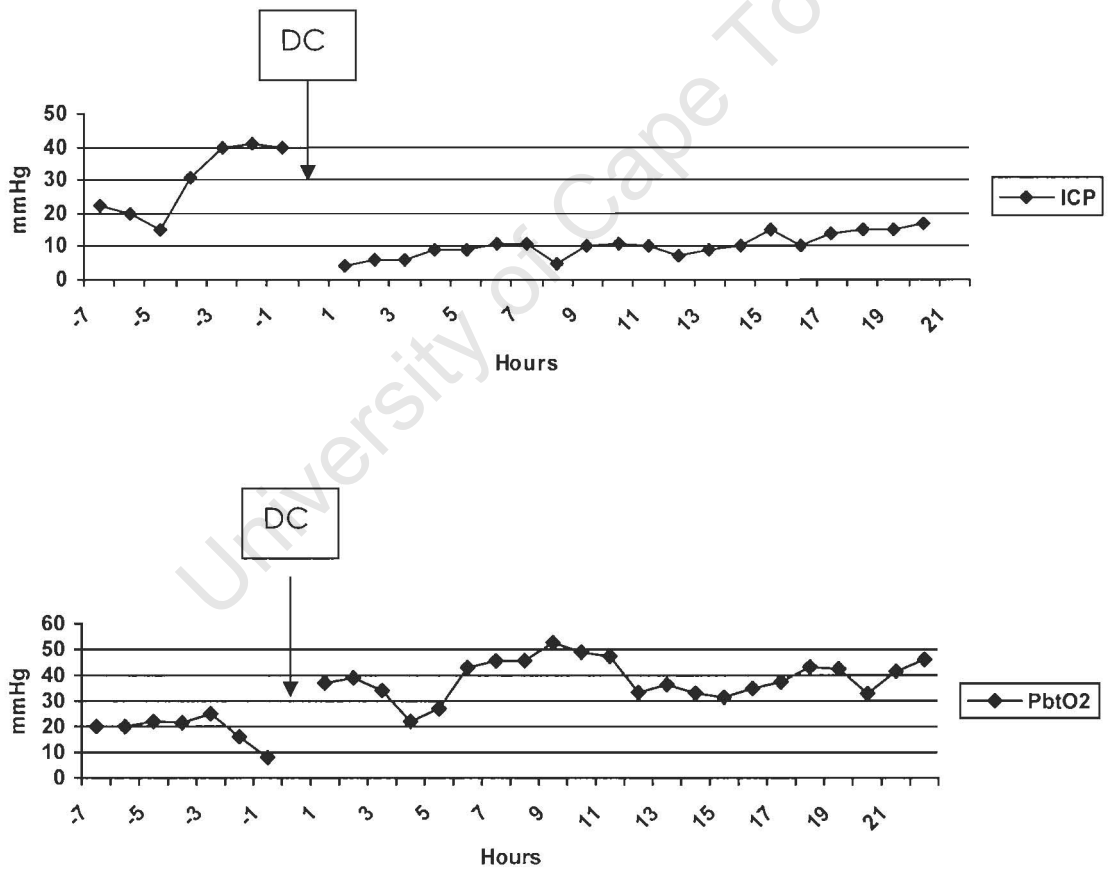

Figure 6: Time course of ICP (above) and PbtO2 (below) before and after decompressive craniectomy (surgery at 0 point)

The immediate postoperative course is shown in Fig 5. Monitoring was continued for 72 hours after surgery, during which time ICP remained controlled and there were no episodes of compromised brain oxygenation (<20mmHg). Over the 72 hours of postoperative monitoring, mean ICP was 10.9 mmHg ± 3.22 (range 4-18), and mean PbtO2 was 53.3 mmHg ± 15.0 (range 22.0 – 86.1). The PbtO2 readings in the upper range (greater than 40 mmHg) in this period, particularly on the second and third postoperative days, may have represented local hyperaemia. No hypodensities or increased oedema were seen in the craniectomised hemisphere on follow-up head CT scan (Fig 3 c+d). Ventilation was continued for 7 days after surgery in large part because of a respiratory tract infection.

The patient's bone flap was replaced 3 months after surgery. At last follow-up (14 months after injury) he had no physical deficits and spoke normally. However, some cognitive deficits remained which eventually required special schooling.

Discussion

This short report examines the ICP and PbtO2 changes after DCH in children with severe TBI. The main findings were that ICP decreased substantially after DCH and that this was accompanied by an immediate and sustained increase in PbtO2 when the preoperative PbtO2 was low. However, changes after DCH depended on the baseline PbtO2 before DCH.

For the 2 patients in whom PbtO2 was >20mmHg before surgery, PbtO2 was initially lower immediately after surgery but recovered so that mean PbtO2 for the 24 hour period was higher than

before surgery. Elevated ICP in these patients before DCH may have been partly on the basis of hyperaemia; however, TCD studies had not been performed during this period.

PbtO2 was compromised (PbtO2 < 20 mmHg) prior to DCH in 4 of 6 whose PbtO2 were analysed. These patients had also required a higher FiO2 to augment brain oxygenation. Each of these patients had episodes of critical hypoxia, with PbtO2<10 mmHg. There was an immediate and significant change in PbtO2 in these patients after DCH. This increase was sustained, and allowed a reduction of FiO2 settings. The immediate change (within minutes of bone removal and durotomy) are apparent in the case illustration.

ICP was markedly reduced by DCH and was sustained. No patient required further thiopentone after surgery.

Conclusion

This study demonstrates the ICP and PbtO2 changes after craniectomy in children with refractory raised ICP. ICP was the most likely factor compromising PbtO2 before craniectomy given the immediate improvement after surgery in patients with low PbtO2. Therefore, although analysis of all data may not reveal a relationship between ICP and PbtO2, elevated ICP may compromise PbtO2 and reduction of ICP, for example with DCH, is associated with changes in PbtO2.

Chapter 16

The Effect of Blood Transfusion on PbtO2 in Children with Severe TBI

Introduction

Anemia in critically ill patients is common. By day 3 after admission to an ICU, up to 95% of patients are anemic [78]. Consequently, the prevalence of RBCT ranges from 14-50% in paediatric ICUs and 20-53% in adult ICUs, depending, in part, on institutional practices and differences in case-mix [21, 402, 403]. For patients who remain in the ICU for longer than a week (e.g. after severe brain injury), up to 85% receive RBCT [78]. The purpose of RBCT is to increase the oxygen-carrying capacity of circulating blood by increasing the Hb concentration with the ultimate goal to improve tissue oxygenation. In healthy humans the critical Hb threshold below which oxygen consumption decreases is unknown, but it is probably below 5 g/dl [177]. Healthy adults are able to increase their cardiac index to compensate for a reduced Hb concentration as low as 5 g/dl after isovolemic hemodilution [410]. This cardiovascular reserve, however, may be lacking in critically ill patients who so develop oxygen-supply dependency; therefore, mortality can be increased in these patients when Hb is less than 6 g/dl [52]. Despite this, the optimal transfusion trigger remains debated [177] because it is yet to be elucidated how to balance the risks of anemia against the known risks of transfusion in individual patients and in particular those with severe brain injury.

In recent years evidence from several clinical studies [139, 212, 217, 295, 361] has resulted in a paradigm shift in transfusion practices in ICUs. Increasing awareness of potential hazards of RBCT has resulted in a more conservative approach to the use of RBCT. A recent systematic review found that in the majority of published studies the risks of RBCT appeared to outweigh the benefits. From pooled data, RBCT

was an independent risk factor for increased risk of mortality, nosocomial infection and acute respiratory distress syndrome with Odd's ratios of 1.7, 1.8 and 2.5 respectively [217]. Others have investigated alternative products that have an oxygen carrying capacity to avoid the risks of RBCT [215, 298]. Today a restrictive transfusion strategy (triggered when Hb is less than 7g/dl) is in common use and recommended for children and adults in the ICU [139, 183]. However, this threshold may not be appropriate for all patients. Patients with acute cardiac disease, for example, appear to benefit from a higher transfusion trigger [140]. In particular, patients with severe TBI may have different transfusion requirements [232] because they are at high risk of secondary cerebral ischaemia. This is supported by experimental evidence that acute hemodilutional anemia aggravates brain oxygenation, increases contusion volume and exacerbates poor outcome in head-injured animals, despite the increase in CBF associated with improved rheology [137]. Acute haemorrhagic anemia also decreases PbtO2 experimentally [216]. RBCT may increase PbtO2 in some adult patients after brain injury but a positive effect of RBCT on PbtO2 is not inevitable [194, 338]. The reasons for this are unclear. Furthermore, the effect of RBCT on PbtO2 in children with TBI has not been studied. Therefore, the purpose of this study was to examine the influence of RBCT on PbtO2 in hemodynamically stable children with severe TBI.

Methods and Materials

Patient selection

Clinical and physiologic data were obtained for children admitted with severe TBI between June 2006 and March 2008, who received ICP, CPP, and PbtO2 monitoring and a RBCT.

Transfusion

Patients who received RBCT and PbtO2 monitoring were included in the study if: 1) > 18 hours had passed since the time of injury, 2) > 12 hours had elapsed since resuscitation, 3) the patient was

haemodynamically stable and no or low-dose vasoactive drugs were in use, 4) inotrope management was not changed in the 6 hours before and 4 hours after RBCT, 5) FiO2 was altered by less than 10% during RBCT and during a 4-hour period before and after transfusion, 6) there was no active bleeding, 7) stable PbtO2 readings had been obtained for at least 4 hours before RBCT, 6) the PbtO2 catheter had been inserted into tissue that appeared normal on CT head scan, and 7) no other RBCT had been given in the preceding 48 hours (a second transfusion in a patient was included for analysis if it was given > 48 hours after the first).

The decision to transfuse patients was made by the attending physician independently from the purposes of this study. In general, RBCT was always given to haemodynamically stable patients with a Hb of < 7g/dl, but the transfusion trigger for individual patients varied based on their clinical condition. The Hb concentration was checked within 6 hours of all RBCTs given. All patients were transfused with packed RBCs depleted of their buffy coat. The additive solution contained saline, mannitol, glucose, adenine and citrate-phospate-dextrose.

Data Collection

For each RBCT given the following data were collected: volume of blood given, Hb concentration before and after RBCT, and age of transfused blood. Since the effect of RBCT varies by height and weight of a patient, particularly for children, the volume given was analysed as volume/body surface area (Vol/BSA). Physiologic data recorded included hourly time-linked variables for PbtO2, CPP and FiO2 for the 4-hour periods before and after RBCT, and 24 hours after RBCT.

Values for PbtO2 before and after RBCT were compared as 3 different time-based variables. First, PbtO2 in the hour before RBCT was compared with PbtO2 in the first hour after RBCT ($PbtO2_{before}$ and $PbtO2_{after}$). Second, all PbtO2 values for the 4-hour period before RBCT were compared with PbtO2 values for the 4-hour period after RBCT ($PbtO2_{4hrs\ before}$ and $PbtO2_{4hrs\ after}$). Third, PbtO2 values immediately before RBCT were compared with PbtO2 24 hours later ($PbtO2_{before}$ and $PbtO2_{24after}$).

CPP and FiO2 values were also documented at each of these time points. The change in each variable after RBCT for each of these variables are reported as ΔPbtO2, ΔCPP, and ΔFiO2 for each of the respective time periods e.g. $\Delta PbtO2_{1hr}$, $\Delta PbtO2_{4hrs}$ and $\Delta PbtO2_{24hrs}$. $\Delta PbtO2_{1hr}$ and $\Delta PbtO2_{4hrs}$ were considered early changes whereas $\Delta PbtO2_{24hrs}$ was considered a late change.

Statistical Analysis

Variables were tested for normality with the Shapiro-Wilk test. Paired t-tests and paired Wilcoxon tests were used to examine differences in physiological variables before and after transfusion. Simple linear regression was then used to examine the effects of physiological, patient and transfusion variables on the difference between PbtO2 values before and after RBCT. Covariates in this model included initial Hb, change in Hb, age of patient, duration of blood storage (age of blood), Vol/BSA, ΔCPP and ΔFiO2. Thereafter, a multiple regression model was constructed using covariates that were significant in the univariate model. A mixed effects regression model was used to test differences between patients and controls in baseline variables and in ΔPbtO2, controlled for ΔCPP and ΔFiO2. Results are reported as mean ± SD (range), or median (interquartile range [IQR] and range) where specified. Spearman's correlation coefficients are reported as r. Significance was set at $p < 0.05$.

Results

Clinical and Transfusion Characteristics

Fifty-one paediatric patients with severe TBI underwent PbtO2 monitoring between June 2006 and March 2008. Thirty-six of these (71%) received a RBCT. Nineteen (53%) of the transfused patients were excluded from analysis for the following reasons: 1) the patient was hemodynamically unstable or significant changes were made to FiO2 (n=10), 2) the PbtO2 catheter was inserted <4 hours before RBCT was started (n=5), 3) transfusion was started before PbtO2 catheters were placed (n=3), or 4) surgery was performed during the study period (n=1). This left 19 RBCTs in 17 patients that were evaluated. Demographic and transfusion variables are listed in Table 1.

Table 1: Demographic, clinical and transfusion variables for patients receiving RBCT (N=17 patients, 19 RBCTs).

Characteristic	Values
Age of patient	5.4 ± 3.4 yrs (0.67-12)
Time of RBCT (median, IQR and range)	2 days (1-3) [1-14]
Initial GCS	5 ± 1 (3-8)
Polytrauma /Isolated TBI	8/9
Initial Hb	8.4 ± 0.8 g/dl (6.8-9.7)
Vol/BSA	312.1 ± 83.8 mls/m² (158-455)
Age of blood (median, IQR and range)	11 days (5-17) [3-28]
Change in Hb after RBCT	2.8 ± 1.1 g/dl (0.7-5.3)

Time of RBCT, time after injury that RBCT was administered; **Vol/BSA**, volume given/body surface area; **Age of blood**, duration of RBC storage, **IQR**, interquartile range. Data are expressed as means ± SD (range) except where specified.

Physiological Variables

The main physiologic variables for transfused patients are summarised in Table 2. Baseline values for the 4-hour period before RBCT were: PbtO2 28.7±6.8 mmHg, CPP 64±15 mmHg, and FiO2 47±13%. Mean baseline PbtO2 before RBCT ($PbtO2_{4hrs\ before}$) was >25mmHg for 12 transfusions, 20-25 mmHg for 6, and <20mmHg for 1.

Table 2: Physiological data. Values for PbtO2, CPP and FiO2 in various time periods before and after RBCT. Asterisks (*) highlight significant differences.

Characteristic	Before RBCT	After RBCT	*p*-value
$PbtO2_{1Hr}$	29.9±8.4 (16.7-44.2)	35.6±11.9 (18.4-59)	0.022*
$PbtO2_{4hrs}$	28.7±6.8 (16.2-39.8)	33.8±11.2 (15.4-59)	0.0018*
$PbtO2_{24Hrs}$	29.9±8.4 (16.7-44.2)	31.6±8.7 (15.6-52.6)	0.433
CPP_{1Hr}	65±17 (38-109)	70±14 (51-104)	0.053
CPP_{4hrs}	64±15 (37-109)	70±13 (47-113)	0.021*
CPP_{24Hrs}	65±17 (38-109)	68±15 (47-96)	0.163
$FiO2_{1Hr}$	47±13 (30-85)	47±12 (30-80)	0.725
$FiO2_{4hrs}$	47±13 (30-90)	47±14 (30-95)	0.474
$FiO2_{24Hrs}$	47±13 (30-85)	46±15 (30-88)	0.454

Change in PbtO2 and Physiological Variables after RBCT

Means for absolute $\Delta PbtO2_{4hrs}$, ΔCPP_{4hrs} and $\Delta FiO2_{4hrs}$ were 5±6 mmHg, 9±10 mmHg, and 0±3% respectively. $PbtO2_{4hrs\ after}$ increased from baseline after 79% (n=15, mean 6.9mmHg) of transfusions and decreased after 21% (n=4, mean -2.6mmHg). Overall, both $PbtO2_{after}$ (p=0.0221) and $PbtO2_{4hrs\ after}$ (p=0.0018) were significantly increased after RBCT (the raw difference was 5.13mmHg for 4 hours after compared with 4 hours before). $CPP_{4hrs\ after}$ was also significantly increased by RBCT (p=0.021) and there was a trend to significance for CPP_{after} (p=0.053). FiO2 changes before and after RBCT

were not significant; however ΔFiO2 had a significant relationship with $\Delta PbtO2_{1hr}$ in univariate analysis, but not with $\Delta PbtO2_{4hrs}$. The change is $PbtO2_{1hr}$ remained significant after controlling for FiO2 changes (p=0.0049).

What influences the ΔPbtO2?

Leal-Noval et al [194] recently suggested that the maximum increment in PbtO2 after RBCT was at 3 hours; therefore the effect of RBCT on $\Delta PbtO2_{4hrs}$ was further examined (Fig 1).

Cerebral perfusion pressure: There appeared to be relationships between the $\Delta PbtO2_{4hrs}$ and both ΔCPP_{4hrs} (r=0.595, p=0.007) and initial Hb (r=-0.47, p=0.042). However, $\Delta PbtO2_{4hrs}$ remained significant when these variables were controlled for (p=0.022 and p=0.006 respectively). When ΔCPP_{4hrs} was 0mmHg ('intercept'), the absolute difference in $PbtO2_{4hrs}$ was 3.2mmHg.

Baseline Hb: For patients with an initial Hb ≤ 8g/dl (n=6) compared with patients with initial Hb > 8g/dl (n=13), Δ $PbtO2_{4hrs}$ was 8.5 ± 7.6 mmHg and 3.6 ± 4.8 mmHg respectively. However, the corresponding CPP changes (ΔCPP 12.1 ± 11.3 mmHg versus 6.4 ± 8.6mmHg respectively) and Vol/BSA given (332±108 mls/m^2 versus 303 ± 73 mls/m^2) were also slightly higher in lower Hb group.

Baseline PbtO2: Higher baseline values of PbtO2 were associated with a larger increase in early PbtO2 compared with patients with lower baseline PbtO2. The correlation between baseline mean $PbtO2_{4hrs\ before}$ and $\Delta PbtO2_{4hrs}$ was 0.607, implying a relationship between baseline PbtO2 and ΔPbtO2, although a definitive conclusion cannot be made based on the confidence interval (CI -0.203-0.924). If baseline mean $PbtO2_{4hrs\ before}$ was below average (PbtO2 28.7mmHg), then $\Delta PbtO2_{4hrs}$ was low, whereas if baseline PbtO2 was above average, $\Delta PbtO2_{4hrs}$ was significant.

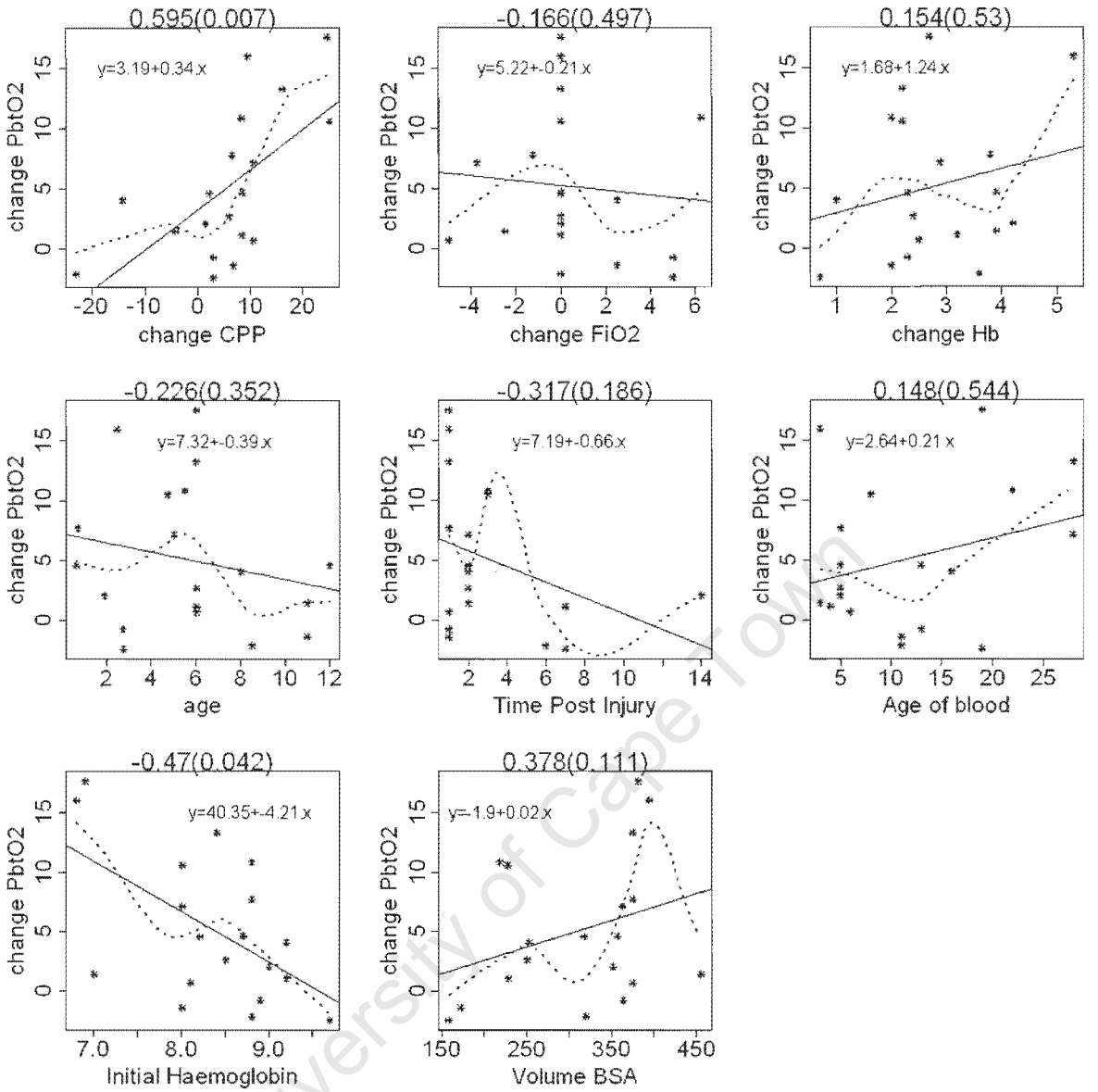

Figure 1: Scatterplot matrix ($\Delta PbtO2_{4hrs}$), fitted simple regression curve and Spearman's correlation (*p*-values) for potential factors influencing the change in PbtO2 with RBCT. Above each box is the corresponding Spearman's correlation coefficient (*p*-value). Regression equation: y=a+b.x where 'a' is the intercept and 'b' is the slope or coefficient for the covariate 'x'.

Age of transfused blood: Duration of blood storage did not have a consistent relationship with ΔPbtO2; suggesting that prolonged storage did not have an adverse effect. However, only 3 patients received blood greater than 19 days old. These patients also tended to have greater CPP changes. In the majority of patients (almost 70%) stored blood was ≤14 days old. Patients receiving older blood tended to have slightly larger changes in PbtO2 (r=0.148, p=0.544). However, the 4 patients whose ΔPbtO2 was negative also tended to receive older blood (see below, Table 3).

Magnitude of RBCT-induced absolute and relative changes in PbtO2: The relative increase of $PbtO2_{4hrs}$ (percentage change from baseline) was 17±21% (range -4 to 58%) and was significantly increased from baseline values (p=0.001). Covariate analysis demonstrated similar results for relative changes and absolute changes, namely that ΔCPP (p=0.02) and initial Hb (p=0.02) influenced ΔPbtO2. Again, the change in PbtO2 remained significant when these changes were considered (p=0.015 and p=0.009 respectively). When significant covariates from univariate analysis were analysed with multiple regression, initial Hb was not a significant predictor (coefficient=-2.81, p=0.07) of absolute ΔPbtO2 and only ΔCPP was significantly associated with absolute ΔPbtO2 in the early period (coefficient=0.26, p=0.02). This association, however, was lost when other variables (ΔHb, patient age, age of blood, Vol/BSA, baseline PbtO2, time post-injury) were introduced into the model (coefficient=0.19, p=0.3). No variables had significant relationships with $\Delta PbtO2_{24hrs.}$ PbtO2, CPP or FiO2 values at 24 hours after RBCT compared with their respective pretransfusion values were similar. The mean $\Delta PbtO2_{24Hrs}$ was 1.7mmHg (p=0.434, confidence interval -2.66-5.88). We did not find any specific predictors for $\Delta PbtO2_{24\ Hrs}$.

Comparison of patients whose PbtO2 increased or decreased after RBCT: When patients with increased $PbtO2_{4hrs\ after}$ (positive $\Delta PbtO2_{4\ Hrs}$) were compared with those with decreased $PbtO2_{4hrs\ after}$ (negative $\Delta PbtO2_{4\ Hrs}$) with respect to baseline values (Table 3), $\Delta FiO2_{4hrs}$ was higher in the negative $\Delta PbtO2_{4Hrs}$ group (p=0.026), which may reflect intervention to increase PbtO2 in these patients. Other factors were similar, although the patients with increased PbtO2 tended to have larger increases in CPP, larger Vol/BSA given, higher baseline PbtO2, and lower initial Hb. However, the number of

episodes where PbtO2 decreased was small (n=4) making it difficult to conclude whether these differences are real or not.

Table 3: Comparison of transfusions with increased $PbtO2_{4hrs}$ (Positive $\Delta PbtO2_{4\ Hrs}$, n=15) after RBCT and transfusions with decreased $PbtO2_{4hrs}$ (Negative $\Delta PbtO2_{4\ Hrs}$, n=4). Values are reported as median (interquartile range).

Characteristic	**Negative $\Delta PbtO2_{4\ Hrs}$**	**Positive $\Delta PbtO2_{4\ Hrs}$**	***p*-value**
$PbtO2_{4hrs\ before}$	24.8mmHg (24.1-28.1)	29.6mmHg (22.5-33.9)	0.774
$\Delta CPP_{4\ Hrs}$	3mmHg (-3.5 - 4)	8.5 mmHg (4-10.5)	0.111
$\Delta FiO2_{4\ Hrs}$	4% (2-5)	0% (-0.625-0)	0.026
Time after injury	3.5 days (1-6.25)	2 days (1-2.5)	0.881
Initial Hb	8.85 g/dl (8.6-9.1)	8.4 (8-8.8)	0.239
Vol/BSA	245.7 mls/m² (169-330)	357.1 mls/m² (251-375)	0.137
Duration of storage	12 days (11-14.5)	6 days (5-17.5)	0.38

Comparison of transfused and non-transfused patients: To examine the possible influence of spontaneous change of PbtO2 with increasing time after injury we matched transfused patients with control patients with severe TBI who did not receive RBCT but received PbtO2 monitoring. Two control patients were matched to each transfusion episode in a study patient by age and the time after

injury of the transfusion. Inclusion criteria for both RBCT and control patients were the same and the same physiologic data obtained during the same time periods after injury were collected in both patient groups. One patient could not be matched for time of transfusion (RBCT received 14 days after injury). Study and control patients appear well-matched (Table 4). There was a significant difference in initial Hb between patients and controls. There were also differences in FiO2 before and after values but ΔFiO2 was similar (p=0.28). There were significant differences between patients and controls for $\Delta PbtO2_{1\ Hr}$ (p=0.021) and $\Delta PbtO2_{4\ Hrs}$ (p=0.025), but no difference in $\Delta PbtO2_{24\ Hrs}$. $PbtO2_{4\ Hrs}$ increased in 79% of transfused patients and 40% of controls. At 24 hours after RBCT, PbtO2 had increased in 62.5% of transfused patients and in 60% of controls. In covariate analysis, $\Delta PbtO2_{4\ Hrs}$ was not significantly different between transfused patients and controls when controlled for $\Delta CPP_{4\ Hrs}$ (p=0.145).

Table 4: Differences in cases (RBCT received) and controls (no RBCT received) for several variables. *Coefficient*, coefficient of the covariate; *CI*, confidence interval. Asterisks (*) denote significant changes.

			95% CI	
Characteristic	**coefficient**	***p* value**	**lower limit**	**upper limit**
Age	0.023	0.89	-0.32	0.37
Time (hours)	-0.34	0.79	-2.95	2.26
Hb Initial	-2.02	<0.0001*	-2.54	-1.49
$PbtO2_{4hrs\ before}$	-3.71	0.12	-8.48	1.07
$PbtO2_{4hrs\ after}$	0.40	0.90	-5.91	6.72
$CPP_{4hrs\ before}$	-1.98	0.52	-8.23	4.27
$CPP_{4hrs\ after}$	3.85	0.24	-2.65	10.35
$FiO2_{4hrs\ before}$	7.67	0.01*	1.95	13.39
$FiO2_{4hrs\ after}$	8.35	0.01*	2.25	14.45
$PbtO2_{24hrs\ after}$	-2.58	0.39	-8.61	3.44
$CPP_{24hrs\ after}$	3.28	0.33	-3.43	10.00
$FiO2_{24hrs\ after}$	5.99	0.13	-1.81	13.80
$\Delta PbtO2_{4hrs}$	4.11	0.025*	0.55	7.67
ΔCPP_{4hrs}	5.80	0.012*	1.37	10.23
$\Delta FiO2_{4hrs}$	0.68	0.28	-0.58	1.95

Discussion

This study examined the influence of RBCT on PbtO2 in children with severe TBI. The main findings were that: 1) PbtO2 increased significantly in the early period after RBCT (in the first hour and over the first 4 hours) compared with baseline pretransfusion values, 2) This effect, however, was lost by 24 hours after transfusion. The results were similar when absolute or relative changes in PbtO2 were examined, 3) When transfused and non-transfused control patients were compared significant differences for the change in PbtO2 were observed in the 1 and 4-hour periods, but not at 24 hours, 4) The magnitude of the change in PbtO2 had a consistent relationship only with the change in CPP, 5) The absolute differences in PbtO2 after RBCT were relatively small (mean difference 5.13mmHg for $\Delta PbtO2_{4\ Hrs}$), particularly when ΔCPP was controlled for (mean difference for intercept 3.19mmHg). In summary, PbtO2 changes were partly influenced by the accompanying change in CPP, were confined to the early period after RBCT, and were larger when baseline PbtO2 was higher and initial Hb was lower.

Methodological limitations

There are a number of possible limitations to this study. First, the sample size is small; therefore these results should be regarded as preliminary. Second, small FiO2 changes were made during the time period of study, and spontaneous fluctuations of CPP occurred; both can influence PbtO2. To reduce the impact of these variables we controlled for changes in CPP and FiO2, had strict eligibility criteria and examined PbtO2 changes over time including a comparison to matched non-transfused controls. It does, however, remain possible that other physiological or therapeutic variables (e.g. minor ventilator settings) that were not controlled for could have influenced the results. Third, spontaneous improvement of PbtO2 over time early after injury may have influenced the results. We therefore excluded RBCT given within 18 hours of injury. Fourth, few patients were less than one year old, which is true in most paediatric head injury series. Therefore, these results best apply to children between the ages of 1 and 15 years. Fifth, 2,3-DPG levels in the RBC packs were not measured;

therefore no direct comment can be made on the effect of reduced 2,3-DPG concentrations on ΔPbtO2. However, it is well known that 2,3-DPG declines progressively with storage and it is almost depleted at 3 weeks [409]. Regeneration of 2,3-DPG levels in healthy volunteers occurs within 24 to 48 hours after RBCT and is most rapid within the first 4-8 hours [116]; therefore we measured both early (4hours) and late (24 hours) effects of RBCT on PbtO2 in this study. Sixth, most patients in this study had baseline PbtO2 greater than 20mmHg. These results therefore may not apply to children with oxygen-supply dependency or reduced cerebrovascular reserve. Seventh, we did not examine the relative risks and benefits of RBCT or its impact on outcome but chose rather to focus on its effect on brain tissue oxygenation.

Adult studies of RBCT and PbtO2

The question of how RBCT influences PbtO2 in paediatric TBI has not been studied. In addition, only 2 centres have addressed this question in adults and these include both TBI and subarachnoid patients [192, 194, 338]. There are some important differences between these studies and the present one. First, the cohort in this study is restricted to paediatric TBI. Second, the inclusion criteria for this study were strict (e.g. FiO2) and attempted to limit the influence of other factors on PbtO2. Third, the data were further examined using matched controls who did not receive RBCT to examine whether time influenced the change in PbtO2. Fourth, physiological data were compared over 4-hour periods before and after RBCT respectively to allow for variability in PbtO2 in both time periods.

Smith et al [338] evaluated PbtO2 after RBCT in adults with TBI and subarachnoid haemorrhage and found that PbtO2 increased in 74% of patients. Only the mean increase in Hb and haematocrit were associated with the change in PbtO2 after RBCT. Leal-Noval and colleagues [194] compared post-transfusion PbtO2 with a single set of pre-transfusion values and found that PbtO2 increased in 78.3% of adult patients with TBI. They found no associations between other variables and the absolute change in PbtO2. The relative change in PbtO2, however, had an inverse relationship with baseline PbtO2, i.e. RBCT was more likely to increase PbtO2 when initial PbtO2 was lower. The

increase in PbtO2 was sustained in 78% of patients with baseline PbtO2 < 15mmHg but in only 45% of those with baseline PbtO2 ≥ 15mmHg, at 24 hours after RBCT. In a subsequent study from this group [192], they also observed an inverse relationship between duration of storage (>19 days) and increase in PbtO2. In the present study, the proportion of patients in whom increased PbtO2 after RBCT was similar to the above studies (79%). In this study however, initial Hb, CPP and baseline PbtO2 were associated with the change in PbtO2 in paediatric patients.

What may influence a PbtO2 response to RBCT?

Baseline PbtO2 and Hb may be important pretransfusion variables that predict a response to RBCT and so need evaluation. For example some studies demonstrate no improvement in tissue oxygenation with RBCT [124, 218, 358, 406]. In part, this may be associated with a lack of an 'oxygen debt' in the subjects examined, i.e. RBCT may only demonstrate improved tissue oxygenation when used in oxygen-supply dependent conditions [116, 389]. This may explain in part why the changes in PbtO2 we observed were relatively small because our exclusion criteria were strict and the likelihood that patients with low PbtO2 received other therapies. However, when we dichotomised the study cohort into a baseline PbtO2 greater or less than25 mmHg we did not observe a greater effect of RBCT on a low baseline PbtO2. In fact the opposite was more likely. This may represent a type II error. However, it is also possible that the ability of RBCT to improve oxygenation in ischaemic tissue is impaired because the greater haematocrit then is associated with increased viscosity and altered capillary erythrocyte flux [358]. Alternatively, since PbtO2 depends in part on a balance between O2 supply and demand, the increase in PbtO2 may appear small since these patients with a low baseline PbtO2 may have a higher oxygen extraction fraction. Consistent with this, Hlatky et al [147] observed that patients at greatest risk for cerebral ischaemia (CBF < 20ml/100g/min and low PbtO2) were the least likely to demonstrate significant PbtO2 increases with normobaric hyperoxia. Finally, there was a greater RBCT effect on PbtO2 when baseline Hb was less than 8g/dl. Tissue oxygenation studies in adults, however, did not observe this relationship [53, 194, 338]. While it may be tempting to use our data to define a "threshold" below which RBCT is beneficial in severe paediatric TBI, caution must be exercised

since the sample size is small and several variables also may play a role, such as volume of blood given and accompanying CPP changes.

Red blood cell storage

Recent studies in cardiac surgery patients and adult males with TBI suggest that blood greater than 14 days or 19 days old respectively may be deleterious or not alter brain oxygen [179, 192]. There are several reasons why "older" transfused blood may be less effective, including decreased erythrocyte deformability, decreased 2,3-DPG, reduced adenosine triphosphate and nitric oxide, increased pro-inflammatory substances, and impaired oxygen 'sensor' in the blood [68, 106, 124, 282]. The data do not allow meaningful conclusions to be made about how the age of transfused blood affects PbtO2 since the majority of transfused blood in this study was < 14 days old (median 11 days) and only 4 transfusions were associated with a decrease in PbtO2. However, there were positive effects of RBCT on PbtO2 even when blood stored for 19 to 28 days was used. It is conceivable that real differences may occur only when blood is stored for longer than 28 days [116] or, alternatively, storage duration may impact tissue oxygenation only in conditions of limited oxygen delivery [282]. Other studies have also failed to demonstrate any adverse effect of duration of storage [282, 386, 387, 406]; therefore, this question remains unresolved.

Conclusion

The results of this study show that RBCT increases PbtO2 in most children (79%) with severe TBI. The overall effect, however, is small, not sustained over time and may result from accompanying changes in CPP. It was not possible to determine why PbtO2 decreased after some transfusions. Further study will be needed to examine the effects of RBCT on PbtO2, the optimal transfusion trigger, and the risk-benefit ratio of RBCT in children with TBI. This is important because, although

cerebral ischaemia must be avoided, strategies that may increase general risk but do not necessarily confer clear benefit should be used with caution.

Chapter 17

The Effects of Normobaric Hyperoxia in Children with Severe TBI

Introduction

PbtO2 is influenced significantly by PaO2, although the PbtO2 response to increased PaO2 varies between patients. The determinants and significance of the magnitude of this PbtO2 response are unclear and the benefits of hyperoxia to the patient are not established as yet. Normobaric hyperoxia has been proposed as a potential therapy for low PbtO2 in TBI, but although there is some evidence to suggest it may be beneficial, it remains controversial. All of the studies of normobaric hyperoxia in TBI have been performed in adult patients. There are no available data for children. This is important because the pathophysiology of childhood TBI differs significantly from that of adults. Furthermore, the risks of hyperoxia in neonatal resuscitation are well known. Therefore, this study aimed to examine the effects of temporary hyperoxia on PbtO2 in children with severe TBI.

Methods and Materials

Patient Selection and Data Collection

Children with severe TBI who received a PbtO2 monitor between June 2006 and May 2008 were included in the study. Daily tests of the PbtO2 monitor function formed part of the protocol for PbtO2 monitoring and were performed by temporarily increasing the FiO2 setting on the ventilator while observing the PbtO2 response. Data from these FiO2 challenge tests were used in this analysis. Test results were included in the study if the following values were recorded: 1) pre- and post-test values

for PbtO2, ICP, CPP, PaO2, SaO2, PaCO2, and 2) baseline values for Hb and TCD FV_{MCA} recorded from the hemisphere containing the PbtO2 monitor. TCD studies were performed using a standard TCD machine and 2 mHz probe (Smart-Lite™, Rimed, Raanana, Israel). TCD studies were performed on the hemisphere ipsilateral to the intracranial catheters to insonate the MCA using a transtemporal approach. The highest mean FV obtained was recorded.

Hyperoxia test

Tests were included in the study only if the patient 1) was hemodynamically stable, 2) had the PbtO2 monitor *in situ* for more than 2 hours, 3) had a stable PbtO2 signal, 4) did not have vasospasm (diagnosed with Lindegaard's ratio)[201], and 5) had a PbtO2 catheter placed in normal-appearing white matter on head CT scan. An arterial sample was taken before the FiO2 increase (before test) and after 15 minutes at the higher FiO2 (after test). The oxygen content (CaO2) of arterial samples was calculated from the equation:

CaO2 (ml O2/100ml) = (Hb x 1.36 x SaO2) + (0.0031 x PaO2)

Differences between before and after test (after 15 minutes at the higher FiO2 level) values were recorded as ΔPbtO2, ΔPaO2, ΔCaO2, ΔPaCO2 and ΔCPP. FiO2 was increased to 100% in most but not all patients. Because the baseline FiO2 also differed between patients, the ratio of the change in PbtO2 for the change in PaO2 (ΔPbtO2/ΔPaO2) was calculated to assess the response of PbtO2 to the change in PaO2. This was termed the oxygen reactivity, and was used as the key variable against which other variables were tested for association. PaO2 is reported in mmHg for consistency and ease of analysis with PbtO2.

Hyperoxia tests for patients in whom PbtO2 catheters were placed in normal-appearing white matter were the primary subject of the study. To complement these results we also compared these to tests in patients in whom catheters had been placed close to contusions on follow-up head CT scan to examine differences in response based on location of the catheter. To limit variability though, further analysis of the data was restricted to catheters placed in normal-appearing tissue.

Statistical Analysis

Variables were tested for normality with the Shapiro-Wilk test. Differences between before test and after test values for PaO2 and PbtO2 were examined with the Wilcoxon's rank sum test. The relationship between ΔPaO2 and ΔPbtO2 was examined with Spearman's correlation and Pearson's product-moment correlation. Correlation co-efficients are reported as r. Linear regression was used to examine the relationship between ΔPbtO2 and ΔPaO2 and ΔCaO2 while controlling for ΔCO2 and ΔCPP.

A general estimating equation (GEE) was used to account for intra- and interindividual differences between tests with catheters placed in normal-appearing brain and those located near contusions for baseline values and ΔPbtO2/ΔPaO2. Linear regression was used to examine the relationship between ΔPbtO2/ΔPaO2 and the following variables: baseline PbtO2, baseline CPP, FV_{MCA}, ΔCaO2, and day of testing (post-injury day; first 24 hours=day 1). ΔPbtO2/ΔPaO2 was further examined for relationships with outcome (GOS) and other indices of low PbtO2 for the whole duration of the monitoring period, which included PbtO2<10, $mPbtO2_{24}$ and lowest PbtO2.

ΔPbtO2/ΔPaO2 was also examined with log transformation because it was assumed to follow a lognormal distribution and hence the log transformed data follow a normal distribution.

Results are expressed as mean ± SD or median and interquartile range (IQR) and range. Significance was set at p=0.05.

Results

A total of 43 tests in 28 patients were performed for which all required data were available. There were 24 patients (35 tests) who had catheters placed in normal–appearing white matter on head CT scans (group A) and 4 patients (8 tests) who had catheters placed close to contusions (Group B). Baseline variables for the Group A are summarized in Table 1. In Group A, baseline PbtO2 was less

than 15mmHg at the time of testing on 3 occasions (3 of 35 tests, 8.5%) and less than 10 mmHg in 1 (1 of 35 tests, 2.9%).

Table 1: Baseline variables for patients with catheters in normal-appearing white matter (Group A).

Characteristic		Value [median (IQR), range or number (frequency)]
Age		5.75 (2.7-7.6) range 9 months to 11 years
Outcome	GOS 1	3 (12.5%)
	GOS 2	0 (0%)
	GOS 3	4 (16.7%)
	GOS 4	7 (29.2%)
	GOS 5	10 (41.7%)
Day of testing		2 (1-3.5) range 1-8
Baseline PaO2		157 (118-186) range 67-332mmHg
Baseline PbtO2		31 (24-37) range 8-81 mmHg
Baseline PbtO2/PaO2 (%)		23 (16-27) range 4-46%
TCD FV_{MCA}		102 (88-117) range 59-154 cm/s
Baseline CPP		68 (61-75) range 42-98 mmHg

Results for baseline variables for tests in patients with catheters in normal-appearing white-matter (n=35 tests in 24 patients). **Day of testing**, post-injury day of the hyperoxia test (day 1= first 24 hours).

PbtO2 in normal-appearing tissue and peri-contusional locations

Patients in Group A and Group B were tested for differences in PaO2, PbtO2, PbtO2/PaO2, ΔPbtO2/ΔPaO2, CPP, and FV_{MCA}. There were no significant differences between tests with catheters placed in normal-appearing tissue (Group A; n=35 tests, 24 patients) and tests with catheters placed close to contusions (Group B; n=8 tests, 4 patients) for PbtO2 (p=0.08), PbtO2/PaO2 (p=0.975), PaO2 (p=0.069) or baseline CPP (p=0.479). In Group B, the FV_{MCA} was slightly lower (median [IQR]: 90 [73-96] cm/s versus 103 [90-123] cm/s; p=0.045). ΔPbtO2/ΔPaO2 was also slightly higher in Group B (median [IQR]: 27.9% [21.9-32.5] versus 14.3% [7.6-22.7]; p=0.049) but not when controlled for baseline PbtO2/PaO2 (p=0.055). These are represented in Figure 1. The remaining results for further analysis below apply to patients in Group A only.

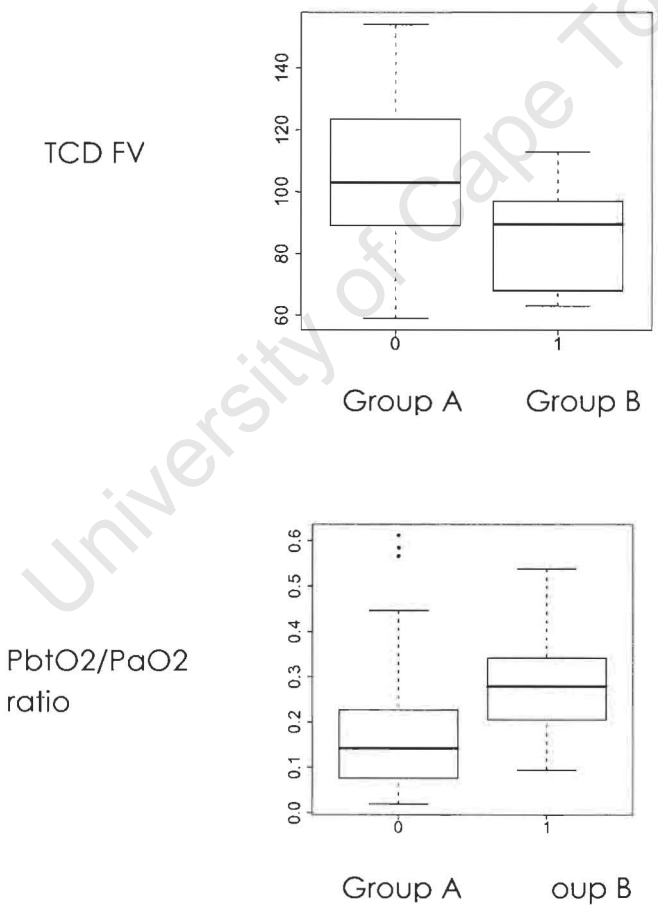

Figure 1: Boxplots for TCD FV_{MCA} (above) and PbtO2/PaO2 ratio (below) for Groups A and B.

Pre- and post test PaO2 and PbtO2 (Group A)

Induced hyperoxia significantly increased both PaO2 (p<0.0001) and PbtO2 (p<0.0001). Baseline PaO2 was 148 ± 59 mmHg and post-test PaO2 was 350 ± 114 mmHg. Baseline PbtO2 was 32 ± 15 mmHg and post-test PbtO2 was 75 ± 59 mmHg. Baseline PaO2 and PbtO2 were not significantly related (p=0.3271). There was a significant relationship between ΔPbtO2 and ΔPaO2 (p<0.0001, R^2=0.371). This relationship was maintained when controlled for ΔCO2 and ΔCPP (p<0.0001, R^2=0.412) during the test. ΔPbtO2 and ΔCaO2 were also significantly related (p=0.001, R^2=0.232).

Relationships with ΔPbtO2/ΔPaO2 (Group A)

ΔPbtO2/ΔPaO2 was significantly related to baseline PbtO2 (Spearman's r=0.538, p=0.001; linear regression p<0.0001, estimate 0.006) (Fig 2). ΔPbtO2/ΔPaO2 was not related to baseline CPP (p=0.209), baseline FV_{MCA} (p=0.596) or ΔCaO2 (p=0.537). There was a trend to significance with day of testing, with higher values found with increasing day after injury (p=0.062, estimate 0.124). There were no significant relationships between ΔPbtO2/ΔPaO2 other indices of low PbtO2 for the duration of monitoring. ΔPbtO2/ΔPaO2 was inversely related to dichotomised outcome, with and without log transformation of ΔPbtO2/ΔPaO2. This relationship remained significant when controlled for baseline PbtO2, day of testing and age (p=0.023, 95% confidence interval 0.032-0.779) (Table2). Therefore, higher ΔPbtO2/ΔPaO2 was associated with a lower probability of good outcome.

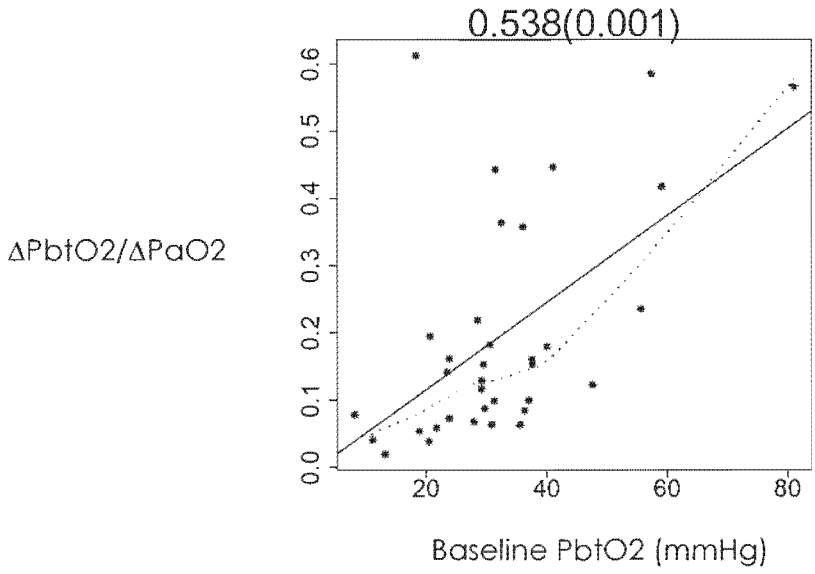

Figure 2: Scatterplot diagram of ΔPbtO2/ΔPaO2 and Baseline PbtO2. Above the box is the Spearman's coefficient (*p*-value).

Table 2: Results of multivariate logistic regression analysis for relationship between variables and dichotomised outcome

	Estimate	StdErr	p-value	95% Confidence Interval
ΔPbtO2/PaO2	-1.839	0.811	0.023	0.03-0.78
PbtO2.1	0.057	0.042	0.170	0.98-1.15
PT day	-0.265	0.231	0.251	0.49-1.21
Age	-0.148	0.152	0.332	0.64-1.16

PT day, day of testing post-trauma. Log transformation was used to create a normal distribution of ΔPbtO2/PaO2.

Discussion

This study examined the effect of increased PaO2 (via temporary increased FiO2) on PbtO2 in children with severe TBI. The main findings were: 1) induced hyperoxia significantly increased PbtO2, (controlled for changes in PaCO2 and CPP), and this increase was closely related to the change in PaO2, 2) the response of PbtO2 (O2 reactivity) was increased with higher baseline PbtO2, 3) an increased response of PbtO2 to PaO2 change was associated with a lower probability of good outcome.

Methodological limitations

There are a number of potential limitations in this study. First, the sample size was small; therefore some significant relationships may not have been demonstrated. However, despite the limited sample size a number of significant results were found. Second, TCD-derived FV_{MCA} was recorded but not local CBF. FV_{MCA} is a useful surrogate marker of changes CBF in the MCA (Chapter 5) but does not necessarily reflect local CBF. Because PbtO2 is a measure of local oxygen tension, local measures of CBF may have been better suited to this study, particularly in regions close to contusions, and may have demonstrated significant relationships between local blood flow and the measured variables. Third, the increase in FiO2 was not standardized. However, PbtO2 changes were interpreted relative to the magnitude of change in PaO2. Fourth, jugular venous saturation was not measured; therefore, no comment can be made on the relationship between PbtO2 and the arteriovenous difference in oxygen content. Jugular venous saturation monitoring was not part of routine clinical practice and global indices of brain oxygenation may not be appropriate to interpret local tissue dynamics. Fifth, cerebral metabolism was not measured; therefore, no comment can be made on whether the observed increase in PbtO2 is beneficial to the tissues. Sixth, a short duration of induced hyperoxia was performed, which was part of our routine testing of the catheter response. Therefore, this study does not report on longer term changes in PbtO2, potential adverse consequences of longer exposure to normobaric hyperoxia, or benefits to the patients. Seventh, there were relatively few tests

that were performed when PbtO2 was low (PbtO2 was less than 10mmHg in only 1 test); therefore, this group could not be examined thoroughly. Finally, the number of patients with poor outcome was relatively small; therefore, other factors related to outcome may not be apparent from these results. Despite these limitations, this is the first study to examine the effects of induced hyperoxia on PbtO2 in children with severe TBI, and demonstrates that hyperoxia consistently increases PbtO2 but that this effect varies depending on baseline PbtO2. The location of the catheter and length of time after injury may be contributing factors.

Determinants of the PbtO2 response

PbtO2 was significantly increased by hyperoxia in this study; however the PbtO2 response relative to the change in PaO2 (ΔPbtO2 / ΔPaO2) challenge varied widely (2-61%). The magnitude of this response was related to baseline PbtO2. These relationships allow for interesting speculation on the physiology on oxygen tension in the microvasculature.

Rosenthal et al demonstrated a dependence of the PbtO2 on the achieved PaO2 with increased FiO2, which in turn was related to lung function [296, 297]. Their results showed a significant relationship between PbtO2 and the product of CBF and cerebral arteriovenous oxygen difference. Even though they used a combination of global and local factors, their results suggested that PbtO2 is more indicative of oxygen diffusion. This is consistent with the views of Menon et al [235] and Bullock [47] that increased oxygen tension in the tissue may overcome diffusion barriers.

This proportional relationship between baseline PbtO2 and oxygen reactivity is in keeping with the results of Hlatky et al [147] who also demonstrated a lower PbtO2 response in patients with low baseline PbtO2 as did Longhi et al [204]. Of note, in the present study the PbtO2 response was not related to FV_{MCA}, whereas in the study by Hlatky et al the PbtO2 response correlated with local CBF. This discrepancy might be explained by the fact that their study examined 2 measures of local physiology while our study correlated PbtO2 with a hemispheral measure of flow velocity.

Of interest was the inverse relationship between ΔPbtO2 / ΔPaO2 and outcome in the present study. One possible explanation is the loss of local O2 reactivity in the microcirculation. The normal

response to increased oxygen tension in the tissues is vasoconstriction [117, 259]; however, this phenomenon may be absent, or even reversed, in injured or ischaemic tissue [330, 415]. A similar phenomenon may also explain different responses of PbtO2 to changes in PaCO2 in injured versus non-injured tissue [89, 131]. Therefore, the increased response of PbtO2 may reflect loss of normal tissue regulatory mechanisms, which may in turn be associated with poor outcome. A similar finding was reported by Van Santbrink et al [393] in adult TBI, in which patients with a lower O2 reactivity had better outcomes. However, low response of PbtO2 in the present study was also associated with low baseline PbtO2, and low PbtO2 is associated with poor outcome. Given the results of the study by Hlatky et al [147], in which patients with apparent ischaemia had the lowest response to hyperoxia, it might have been expected that a low response to hyperoxia would have been associated with poor outcome in our results. A possible reason for this is that very few patients that were tested had low baseline PbtO2. It is possible that both very high and very low PbtO2 responses to hyperoxia may be associated with poor outcome, but are measures of different processes. These data do not allow further clarification though.

Does normobaric hyperoxia benefit cerebral metabolism?

The issue of the potential benefits of hyperoxia continues to be debated. On one hand, it is argued that increased oxygen tension only produces a small increase in arterial oxygen content. Physiologically dissolved oxygen in the plasma only represents 2-3% of overall oxygen transport [236]. If arterial blood is near full saturation, hyperoxia does not substantially improve oxygen delivery to the tissues. Therefore, although hyperoxia increases tissue oxygen tension it may not improve oxygen delivery to the brain, particularly under conditions of brain ischaemia [303]. On the other hand, increased oxygen tension in the tissues may improve mitochondrial function in ways not yet fully understood [47]. For example, PO2 decreases nonlinearly in the extracellular space with increasing distance from the vessel [313]. Therefore, increased oxygen tension in the capillary may improve the diffusion of oxygen in conditions where diffusion barriers are increased due to cytotoxic cell swelling, perivascular edema, collapsed capillaries and arteriovenous shunting in the microvasculature [235]. In these conditions, diffusion-limited ischaemia may be as important as perfusion-limited ischaemia. Also, dissolved

oxygen may be preferentially used for tissue oxygenation [133, 358]. Unfortunately, tissue most at risk of brain ischaemia demonstrates the lowest response of PbtO2 to hyperoxia [147] and hypoxic tissue may have limited ability to increase oxygen extraction [235].

Several clinical studies in adult patients with TBI have attempted to define the effect of normobaric hyperoxia on brain tissue metabolism but the results have been conflicting [91, 211, 263, 289, 290, 373]. Tolias et al [373] demonstrated a reduction in the lactate/pyruvate ratio with normobaric hyperoxia, but a study by Magnoni et al [211] showed a similar reduction in lactate but no improvement in the lactate/pyruvate ratio. Diringer et al [91] performed a PET study in 5 patients and failed to detect an improvement in global measures of CMRO2 with hyperoxia. However, a later study by Nortje et al [263] examined local regions with PET and demonstrated an improvement in tissue at risk for ischaemia. The effect of hyperoxia may depend in part on the nature of the ischaemic insult. For example, in rats with ischaemia induced by MCA occlusion, hyperoxia reduced infarct size and improved outcome [202, 330] while in dogs worse outcome was observed with hyperoxia after cardiac arrest [400].

What are the potential hazards of normobaric hyperoxia?

Potential hazards of hyperoxia include the generation of oxygen reactive species, lung atelectasis and inflammation, pulmonary vasoconstriction, breakdown of the blood brain barrier, and haemorrhage into infarcts. In trauma patients it appears that acute lung injury worsens prognosis [324]. Also, in neonates in particular, there are substantial concerns about the effects of hyperoxia on DNA damage and injury to the developing brain [342]. However, in older patients short term exposure (<24 hours) to normobaric hyperoxia is probably well tolerated with few adverse effects [330] and does not appear to increase free radical production in the injured brain [94].

Although hyperoxia may cause reduction in CBF in normal brain, these reductions are thought to be small if hyperbaric hyperoxia is not used [330]. Furthermore, CBF reductions are not always observed, and when they do occur they may in part be explained by concomitant reductions in PaCO2 [49]. Even if cerebral vasoconstriction does occur, this may redirect blood from relatively normal to ischaemic

territories. Experimental studies have shown *improved* CBF and oxygenated hemoglobin in ischaemic core and penumbral tissue [330]. Different microvasculature responses to increased oxygen tension and a reduction in metabolic burden due to decreased peri-infarct depolarisation may in part explain these findings.

Conclusion

Similar to adults, normobaric hyperoxia significantly increases PbtO2 in children with severe TBI in normal-appearing brain tissue. There was a wide range in the response of PbtO2 to increased PaO2. The magnitude of this response was significantly related only to baseline PbtO2. Of interest, patients with a poor outcome tended to have higher PbtO2 responses to a PaO2 challenge, which may reflect disturbances of local circulatory responses to changes in PaO2.

Chapter 18

Transcranial Doppler Flow Velocities and Relationships with Clinical and Physiological Variables

Introduction

TCD studies of the FV_{MCA} are potentially useful to monitor cerebral hemodynamics non-invasively and help interpret perturbations in other monitored variables such as ICP and PbtO2. However, few studies have reported the relationship between TCD parameters and PbtO2, and these have been performed in adult patients [89, 392]. Also, the TCD-derived pulsatility index (PI) has been reported to be closely associated with ICP and CPP in adult TBI, but little is known about these relationships in paediatric TBI (Chapter 5). These are important issues because cerebral hemodynamics differ in childhood TBI compared to their adult counterparts. Therefore, this study aimed to examine the relationships between TCD-derived parameters and clinical and physiological variables in children with severe TBI. Specifically, it examines 1) the relationships between FV_{MCA} and clinical and physiological variables, 2) the incidence of vasospasm in paediatric severe TBI, 3) the relationship between the pulsatility index and ICP and CPP.

Methods and Materials

TCD studies performed on patients with severe TBI were recorded and analysed. All studies were performed by one investigator (the author) as a bedside investigation using a standard TCD machine (Smart-lite™, Rimed, Raanana, Israel) with a 2MHz probe. The MCA was insonated on both sides where possible. Optimal depth of insonation of the MCA varied by age and other physical factors such

as scalp swelling. Recorded parameters included peak, mean and diastolic FV and PI. The highest recorded mean FV_{MCA} was used for all analyses with other variables. The PI was calculated as the Gosling index [126] which is the difference between the systolic velocity (FV_s) and the diastolic velocity (FV_d) divided by the mean FV_{MCA}:

$$\mathbf{PI = (FV_s - FV_d) / FV_{mean}}$$

For general analysis with clinical variables (Group A), TCD recordings were included in the study if 1) no changes to ventilatory parameters had been made in the preceding 2 hours, and 2) PaCO2 was in the range of 30 to 45 mmHg. For comparison with selected physiological (ICP and PbtO2) variables (Group B), TCD studies were included if 1) the study was performed on the MCA ipsilateral to the intracranial catheters, 2) vasospasm was not present, 3) ICP, MAP and PbtO2 data at the time of the study were recorded, and 4) the PbtO2 catheter had been placed in normal-appearing white matter on head CT scan. The influence of PaO2 on the PbtO2 value was considered by comparing FV_{MCA} to the PbtO2/PaO2 ratio rather than absolute PbtO2. Studies detecting vasospasm were also excluded from analysis of PI.

Vasospasm was defined according to the criteria of Lindegaard [201]. The Lindgaard ratio was calculated by dividing FV_{MCA} by FV in the ipsilateral extracranial internal carotid artery. Vasospasm was diagnosed if this ratio was >3 and FV_{MCA} was >120 cm/s. Studies with vasospasm were identified and excluded from analysis as was appropriate.

Statistical analysis

Normality of data was tested with the Shapiro-Wilk test. Spearman's correlation coefficient was used to test general correlation between means of variables, but a general estimating equation (GEE) and linear mixed effects (LME) models were used to account for inter- and intra-individual differences between studies using original observations. Data were tested for associations between FV_{MCA} and 1) clinical variables (initial GCS, age, CT classification, day of testing, and outcome) [Group A], 2) selected physiological variables recorded at the time of the study (ICP, PbtO2, CPP, PaO2, PaCO2)

[Group B], and 3) markers of secondary insults for the duration of ICU stay (ICP>20mmHg, ICP_{peak}, and PbtO2<10mmHg) [Group A].

Outcome (Group A): FV_{MCA} was tested against the GOS for the patient as an ordinal (GOS 1 to 5) and dichotomous variable (GOS 1 to 3, and GOS 4 to 5) controlled for the day of testing (post-trauma day).

Physiological variables (Group B): FV_{MCA} was tested for associations with selected physiological variables such as ICP, MAP, PbtO2 and PaCO2 data using GEE. These values were recorded at the time of the TCD study and were tested against FV_{MCA} as a continuous and dichotomous (FV_{MCA} < 120cm/s and FV_{MCA} ≥120cm/s) variable.

PI (Group A): Correlation and GEE were used to examine the relationship between PI and ICP and CPP at the time of the TCD study.

Data are expressed as means ± SD or median and interquartile range (IQR). Significance was set at p=0.05.

Results

A total of 291 hemispheric TCD recordings performed in 34 patients met the criteria for entry into the study. Vasospasm was detected in 4 studies in one patient, which were excluded from further analysis. This left 287 studies (34 patients) which were used for general analysis (Group A). Of the remainder, 115 recordings (27 patients) fulfilled the criteria for examination with selected physiological variables from catheters placed ipsilateral to the side of the TCD examination (Group B). Table 1 summarises important variables.

Table 1: Clinical, TCD and physiological variables

Characteristic	Value [median (IQR) range]
Age	6.5 (3.5-8.6) range 0.75-14 years old
Initial GCS	6 (5-7) range 3-8
FV_{MCA}	95 (79-115) range 32-180cm/s
PI	0.78 (0.65-0.92) range 0.31-1.42
ICP	13 (9-19) range 1-42 mmHg
CPP	97 (61-80) range 31-105 mmHg
Outcome	
GOS 1	3
GOS 2	0
GOS 3	6
GOS 4	13
GOS 5	12
Day of testing (post-trauma day)	3 (2-4) range 1-10
PbtO2 (Group B)	28 (24.8-39) range 13-84 mmHg
PbtO2/PaO2 (%) (Group B)	23 (15-32) %

Patients n=34; number of studies, n=287 (Group A) unless specified otherwise. PbtO2/PaO2 is expressed as the percentage PbtO2 of concurrent PaO2.

TCD and General Variables (Group A; n=287 TCD studies, 34 patients)

Demographic/Clinical variables: There were no significant associations between FV_{MCA} and initial GCS (p=0.673), age (p=0.120) or initial CT classification (p=0.983) with GEE. However, age had a significant inverse relationship with FV_{MCA} when only studies from Day 1 were considered (p=0.0002, r=-0.4883), i.e. FV_{MCA} was higher in younger patients in the first 24 hours after injury. There was no

significant relationship between FV_{MCA} and the day of testing (post-trauma day) (GEE p=0.490) in general. However, when the first 2 days were compared, FV_{MCA} was significantly lower in the first 24 hours (90 ± 25 cm/s on Day 1 versus 106 ± 25 cm/s on Day 2, p=0.01). FV_{MCA} was highest on day 2 (106 ± 25 cm/s) and lowest on day 5 (83 ± 15 cm/s).

Markers of secondary insults: FV_{MCA} had a marginal relationship with ICP_{peak} (p=0.049) but not with ICP>20 (p=0.328) and PbtO2<10 (p=0.369).

Outcome: The relationship between FV_{MCA} and outcome was examined for of each day from day 1 to day 6. Beyond day 6 there were too few observations to analyse meaningfully. There was no overall relationship between FV_{MCA} and outcome (p=0.401). There was no relationship when other post-trauma days were examined separately, with outcome as a dichotomous (p=0.092 to 0.732, day 1 to 6) or as an ordinal variable (p=0.19 to 0.71, day 1 to 6).

Pulsatility Index (n=287 TCD studies)

Examination of means demonstrated a significant relationship between PI and ICP (Spearman's r=0.358, p=0.038). However, when the original observations were used and differences within individuals was accounted for (GEE), there was no significant relationship between P.I. and ICP (p=0.229, intra-class coefficient 0.460). Binary examination of PI (PI <1 and ≥1) also showed no relationship with ICP (p=0.471).

There was, however, a significant relationship between PI and CPP with examination of both means and original observations (GEE p=0.001) (Fig 1). However, there were too few observations of low CPP to test the sensitivity and specificity of the clinically important CPP threshold at 50 mmHg.

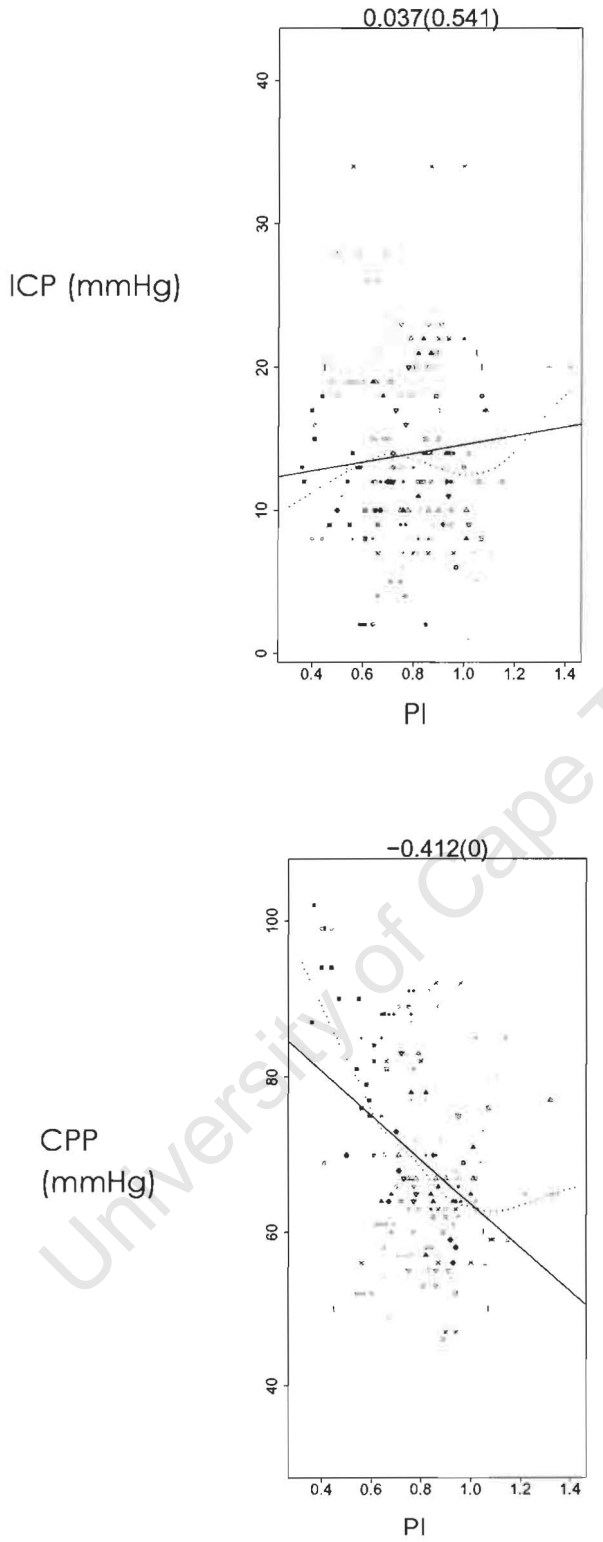

Figure 1: Scatterplots for ICP (above) and CPP (below) against PI. Spearman's r (*p*-value) above box.

Relationship Between FV_{MCA} and Selected Physiological Parameters (Group B; n=115 TCD studies, 27 patients)

PbtO2: When FV_{MCA} was examined as a continuous variable, there was a trend towards an association of higher FV_{MCA} with higher PbtO2/PaO2 values for all recordings but this was not significant (LME, p=0.081, estimate 40.532) when controlled for PaCO2 and CPP. However, when data from day 1 were examined only, FV_{MCA} was significantly correlated with PbtO2/PaO2 (p=0.006, estimate 367). The overall relationship was also significant when FV_{MCA} was examined as a dichotomous variable with logistic regression for all days tested. The PbtO2/PaO2 ratio was significantly higher in patients who had FV_{MCA} ≥120cm/s (p=0.024).

PaCO2, CPP, and ICP: PaCO2 (p=0.33) and CPP (p=0.53) were not related to FV_{MCA}. There was a significant relationship between ICP and FV_{MCA}, even when controlled for PaCO2 and CPP (p=0.003). However, there was no significant difference in ICP when studies with FV_{MCA} ≥120cm/s or <120cm/s (p=0.318) were compared.

Vasospasm

Vasospasm (Lindegaard ratio>3 and FV_{MCA} was >120 cm/s) was only detected in 1 of 34 patients (3%). Of the 4 studies in which vasospasm was diagnosed in this patient, PbtO2 was not less than 20mmHg at any time. However, for this patient PbtO2 was in general higher in other TCD studies for this patient where there was no vasospasm than in the above-mentioned 4 studies. Overall, FV_{MCA} >120 cm/s was found in 16% of all studies (n=48) but these did not fulfil criteria for vasospasm.

Discussion

This study examined children with severe TBI for relationships between TCD-derived parameters and 1) general clinical variables (age, initial GCS, markers of secondary intracranial insults, outcome and day of testing), and 2) physiological parameters recorded at the time of the TCD study. The main findings were: 1) FV_{MCA} was significantly lower on day 1 compared to day 2, 2) FV_{MCA} was not demonstrated to be associated with outcome on any of the days of testing, 3) there were no other relationships between FV_{MCA} and general clinical parameters apart from a marginal relationship with maximum ICP experienced by the patient, 4) PI index was not related to ICP, but was there was a significant inverse relationship between CPP and PI, 5) higher FV_{MCA} was associated with a higher PbtO2/PaO2 (particularly on day 1) and higher ICP, 6) although 16% of studies showed FV_{MCA} >120cm/s, vasospasm was uncommon and was only diagnosed in 1 patient (3%).

FV and physiological variables

The finding of a positive correlation between FV_{MCA} and ICP is at odds with the inverse relationship between CBF (measured by the Kety-Schmidt technique) and ICP in a study by Sharples et al [329]. It is not immediately apparent what the explanation for this difference is. One possibility is that TCD FV is a surrogate marker of CBF and does not measure actual CBF, although the relationship between the 2 measures should be reliable (Chapter 5), particularly if vasospasm is excluded as was done in this study. Another possible reason may relate to the fact that the patients reported by Sharples et al were electively hyperventilated (lowest PaCO2 2.1 kPa) and CBF results were not corrected for PaCO2. All TCD recordings in the present study were performed in the normocapneic range and higher FV_{MCA} tended to be associated with higher ICP and higher PbtO2/PaO2, which may reflect a tendency towards hyperaemia, or hypermetabolism, with increased cerebral blood volume in some patients. Lower FV_{MCA}, especially on day 1, was associated with low PbtO2/PaO2; however, we did not demonstrate a clear relationship between FV and outcome; although others have demonstrated that low CBF correlates with poor outcome (Chapter 5). The lack of relationship in the present study may relate to the variability of normal CBF levels for age. The numbers in this study were likely too small to demonstrate a significant result while controlling for day of testing and age. The association between

early low CBF and poor outcome may reflect mitochondrial dysfunction and depressed cerebral metabolism as much as it may reflect ischaemia [401]. The combination with low PbtO2 (as in this study) though, may suggest ischaemia or failure of local microcirculatory regulation.

Two studies have examined TCD flow velocities and PbtO2 in adult patients with TBI. Van Santbrink et al [392] found a strong correlation between FV_{MCA} and PbtO2 values (R=0.73) in adult TBI patients within 8 hours of injury, but no correlation beyond this period. Dings et al [89] found that PbtO2 paralleled the time course of FV_{MCA} after injury in adult patients. The results of our study are consistent with these reports.

Pulsatility Index

The relationship between PI and ICP was not significant in the present study. This is in contrast to several studies that have reported significant relationship between ICP and PI in adult TBI (Chapter 5). In paediatric TBI, therefore, PI is an unreliable guide for the estimation of absolute ICP. The reasons for this are unclear, but may involve the differences between adult and paediatric TBI in cerebral hemodynamics and pressure-volume index [325]. Alternatively, accounting for intra-individual differences (as was done in this study with GEE) may yield different results compared to the adult studies. A potential limitation may be that relatively few studies were performed when ICP was elevated above 20mmHg. The relationship between PI and ICP above 20 mmHg may be different. Also, our data cannot exclude that PI may still be a useful guide to relative ICP in an individual patient and other causes of elevated ICP, such as hydrocephalus, may demonstrate different relationships between ICP and PI. However, our results do suggest that PI may still be useful in the non-invasive assessment of CPP compromise in children with severe TBI. These results are consistent with the results of Chan et al in adult patients with TBI [60]. The data are not specific enough to identify a threshold value of PI for CPP<50, nor have we calculated sensitivity or specificity for PI in relation to CPP. However, this suggests that further studies are warranted because TCD is widely available and is non-invasive. Therefore, it may be of benefit in the acute assessment of patients who have not yet

had an ICP monitor inserted or in patients with mild-moderate TBI who are not being monitored but may be at risk of deterioration.

Vasospasm

Vasospasm was uncommon in this study, which is consistent with the results of Mandera et al [213]. Based on their report and ours, it appears that vasospasm is less common in children than in adult TBI [227, 228, 419]. The reasons for this are unclear but warrant further study. One potential limitation is that only the FV_{MCA} was used to detect vasospasm. It is possible that a higher incidence may have been found with insonation of all the basal vessels. Also, 16% of the studies demonstrated $FV_{MCA} \geq$ 120cm/s. Whether this represents true hyperaemia or CBF coupled with increased metabolism, is unclear and also needs to be clarified. The distinction between vasospasm and increased flow in the MCA though, should be clear.

Conclusion

This study examined the relationships between TCD parameters and demographic, clinical and physiological variables in children with severe TBI. PI is not a reliable indicator of absolute ICP in children with severe TBI; however, higher PI is associated with lower CPP. Higher FV_{MCA} was associated with higher PbtO2 and ICP values. Vasospasm was uncommon. Of note, the range in FV_{MCA} was very wide (32-180cm/s), which emphasizes major potential differences between individuals with TBI and may argue against uniform treatment of all patients with strict treatment targets, while supporting the individualisation of treatment.

Chapter 19

Pressure Autoregulation in Paediatric TBI

Introduction

Pressure autoregulation (AR) may be impaired after TBI; however, monitoring or testing autoregulation as part of a protocol for treating patients with TBI is not common practice in the paediatric ICU, despite the significance implications that the status of AR may have on therapies in the ICU (Chapter 5). Even though the role that AR may play in the pathophysiology of TBI in children is being increasingly appreciated, few studies of practical approaches to testing AR in the paediatric critical care unit have been published to date. Also, the impact of the status of AR on physiological parameters, such as ICP and PbtO2, in paediatric TBI has not been examined. Therefore, this study aimed to examine 1) the prevalence of impaired AR, 2) the associations of impaired TBI with clinical parameters, and 3) the impact of BP changes on ICP and PbtO2 in paediatric severe TBI with respect to the status of AR in the practical setting of a paediatric ICU.

Methods and Materials

AR testing was part of the clinical management of patients. Information from these tests was used to assist clinical decisions about the impact of raising or lowering BP. For example, awareness of the effects of increased BP on ICP and PbtO2 informed decisions about whether increasing BP was advisable as a therapeutic intervention for low PbtO2. Simple observation of the relationship between BP and ICP is inadequate for this purpose because the 2 factors interact in different ways. Elevated BP may increase ICP if AR is impaired. Conversely, increased BP may occur secondary to elevated

ICP due to a Cushing's response. Therefore, the safety and effectiveness of a therapeutic protocol to elevate MAP to improve ICP control and reduce the risk of ischaemic episodes, such as that recommended by Rosner et al [300] is not clear in absence of knowledge about the status of AR.

Protocol for AR testing

The method employed for testing the strength of AR was similar to that described by Vavilala et al [397], in which a titrated phenylephrine infusion is used to elevate MAP by 20% of the baseline value. Before MAP was elevated, baseline recordings were made of MAP, ICP, PbtO2 and FV_{MCA}. Although both sides were insonated in most patients, only recordings taken from hemispheres ipsilateral to the ICP and PbtO2 monitors were analysed. When the MAP increase reached 20% of its baseline value, the ICP, PbtO2 and FV_{MCA} were again recorded. Thereafter MAP was returned to its baseline value and recordings were repeated for a final time. Testing was only performed when PaCO2 was in the range of 30mmHg to 45mmHg.

An autoregulatory index (ARI) was calculated based on the response of FV_{MCA} to elevated MAP according to methods previously described [268]. The equation used to calculate ARI is:

ARI = %ΔeCVR / %ΔMAP or %ΔCPP (depending on whether ICP is being monitored).

eCVR is the estimated cerebrovascular resistance and is the ratio of MAP/ FV. ΔeCVR and ΔCPP were calculated as the difference between the values at baseline and after elevation of MAP. An ARI value of 1 implies that the strength of AR is maximal, a value of 0 implies complete absence of AR, and values between 0 and 1 reflect the relative strength of AR. Although the AR capacity is a continuum, an ARI of 0.4 is commonly used as a threshold to describe whether AR is intact or not. Values for ARI <0.4 are associated with impaired AR and values ≥0.4 are associated with intact AR [380].

Statistical Analysis

Variables were tested for normality with the Shapiro-Wilk test. Spearman's and Pearson's correlation coefficients were used to test the correlation between ARI and 1) demographic and clinical factors (age, day of testing post-injury, initial GCS), 2) baseline physiological variables (MAP, ICP, CPP, PbtO2) and 3) the change in physiological variables with testing (ΔMAP, ΔICP, ΔPbtO2). Linear regression was used to test these variables against ARI as a continuous variable and logistic regression was used to test the variables against dichotomised ARI (<0.4 and ≥0.4). Variables significant in univariate analysis were then tested in multivariate analysis.

ARI (continuous and dichotomous) was also tested against the GOS as a dichotomous score with logistic regression (GOS 1 to 3 as unfavorable outcome, and GOS 4 to 5 as favorable outcome), and as an ordinal score (GOS 1 to 5) with a proportional odds regression model. When testing for associations between ARI and outcome only the worst ARI for each patient was used.

Data are expressed as means ± SD or median and interquartile range (IQR). Significance was set at p=0.05.

Results

Fifty-two AR tests for which all data were available were performed in 24 patients with severe TBI. Average patient age was 6.3 ± 3.2 years old (range 1 to 11). Median postresuscitation GCS was 6 (IQR 4 to 7, range 3 to 8). Mean baseline ICP, CPP and PbtO2 before testing were 13 ± 5mmHg, 67 ± 14 mmHg, and 28.3 ± 13.9 mmHg. Sixteen tests (31%) were performed within the first 24 hours of injury. Median day of testing after injury was day 2 (IQR 1 to 3, range 1 to 7). Four children (17%) had AR tested once during their stay in the ICU; all others had AR tested twice or more. AR was impaired (by the definition of ARI<0.4) in 29% of patients (n=7) at some point during their ICU stay. There was

no association between ARI and time after injury (p=0.97).There was no relationship between ΔMAP and ΔICP across all tests (p=0.54).

ARI compared with clinical and physiological variables

Relationships between ARI as a continuous variable and clinical and physiological factors are summarised in Table 1. Differences between variables for tests with impaired AR (ARI<0.4) and intact (ARI≥0.4) groups are shown in Table 2. Baseline values for ICP, PbtO2, MAP and FV_{MCA} were similar in the 2 groups.

ICP: ARI (continuous and dichotomous) was significantly associated with ΔICP (continuous ARI, p=0.003, r=-0.044). ΔICP was inversely associated with ARI, i.e. higher ARI values were associated with no ICP change or a reduction in ICP when BP was increased, while lower ARI values were associated with increased ICP (Table 1 and 2). When ARI was ≥0.4, median ΔICP was -0.5 (IQR -2 to 0) mmHg and when ARI was <0.4, ΔICP was 2.9 (IQR 0 to 3.3) mmHg. When ARI was ≥0.4, ICP increased with testing in 4/43 tests (9%) compared with no increase or reduction in ICP in 39/43 tests (91%). By comparison, when ARI was <0.4 ICP increased in 7/9 tests (78%) and decreased in 2/9 tests (22%).

PbtO2: ARI (continuous and dichotomous) was also inversely associated with ΔPbtO2 (continuous ARI, p=0.001, r=-0.087). However, the changes in PbtO2 were less limited by the ARI dichotomised categories. PbtO2 increased in most cases when BP was increased; however, the magnitude of this response remained significantly related to the strength of ARI (Table 1 and 2). When ARI was ≥0.4, median ΔPbtO2 was 1 (IQR 0 to 2.2) mmHg and when ARI was <0.4, ΔPbtO2 was 4 (IQR 2.9 to 4.2) mmHg. When ARI was ≥0.4, PbtO2 increased with testing in 30/43 tests (70%) compared with no increase or reduction in PbtO2 in 13/43 tests (30%). By comparison, when ARI was <0.4 PbtO2 increased in 9/9 tests (100%). When compared with the tests in which ARI was ≥0.4 *and* ICP decreased or remained unchanged, PbtO2 still increased in 67% of cases (26 of 39 tests).

Initial GCS: Initial GCS was significantly associated with ARI (p=0.017, r=0.056). Specifically, patients with an initial GCS of 3 were more likely to have a low ARI. Baseline FV_{MCA}, baseline ICP and age were included into the multivariate model because of clinical relevance. Initial GCS was an

independent predictor of ARI in multivariate analysis in this model (p=0.03, R^2=0.002). The binary point of best discrimination for initial GCS was an ARI of 0.68 (p=0.008).

Table 1: Linear regression results for ARI and clinical and physiological factors

	Estimate	**StdErr**	**P-value**	**95% CI**
Day	-0.001	0.027	0.967	-0.054 to 0.052
Baseline FV	-0.001	0.001	0.608	-0.003 to 0.002
Baseline ICP	-0.005	0.007	0.453	-0.019 to 0.009
Baseline PbtO2	-0.000	0.003	0.862	-0.006 to 0.005
Baseline MAP	-0.000	0.003	0.929	-0.006 to 0.005
Δ MAP	-0.001	0.004	0.878	-0.009 to 0.008
ΔICP	-0.044	0.015	0.003*	-0.074 to -0.015
ΔPbtO2	-0.087	0.026	0.001*	-0.138 to -0.035
Mean PbtO2	0.002	0.003	0.604	-0.004 to 0.008
Mean ICP	0.006	0.008	0.453	-0.010 to 0.022
Mean CPP	0.006	0.004	0.159	-0.002 to 0.014
PbtO2/PaO2	-0.061	0.412	0.881	-0.868 to 0.746
Initial GCS	0.056	0.024	0.017*	0.010 to 0.102
Age	0.005	0.013	0.727	-0.021 to 0.030

Day, day of testing after injury (first 24 hours=day 1); **baseline FV**, baseline TCD FV_{MCA}; mean PbtO2, mean ICP and mean CPP refer to mean values for the duration of monitoring for each patient; Std Err, standard error of the mean. Baseline values refer to physiological parameters immediately before testing. Significant results are denoted by *.

Table 2: Differences in physiological factors in 2 groups for tests with ARI results dichotomised (median, IQR)

	ARI<0.4	**ARI≥0.4**	***p*=value**
ΔICP (mmHg)	2.9 (0 to 3.3)	-0.5 (-2 to 0)	0.019*
ΔPbtO2 (mmHg)	4 (2.9 to 4.2)	1 (0 to 2.2)	0.019*
Baseline ICP (mmHg)	16.8 (13-19)	13 (9-17)	0.164
Baseline PbtO2 (mmHg)	28.3 (23-29)	28.6 (25-36)	0.578
PbtO2/PaO2 (%)	19.2 (14-23)	19.2 (13-28)	0.890
Baseline MAP (mmHg)	79 (77-85)	79 (70-94)	0.905
Baseline FV_{MCA} (cm/s)	93 (84-129)	104 (84-121)	0.808

PbtO2/PaO2, ratio between PbtO2 and concurrent PaO2, expressed as a percentage.

ARI and Outcome (n=24 patients)

The relationship between ARI and outcome was explored in a number of ways, using combinations of ARI as the independent continuous and dichotomous variable and outcome (GOS) as the dependent ordinal and dichotomous variable. No relationship between ARI and outcome was found (range of *p*-values 0.243 to 0.662).

Discussion

This study examined associations between the indices of AR (determined by the TCD-derived FV_{MCA} response to elevation of MAP) and clinical and physiological factors in children with severe TBI. ARI was calculated as an index of the strength of AR. The main findings were 1) impaired AR was demonstrated in approximately 30% of patients, 2) low ARI was associated with low initial GCS, 3) when AR is weak ICP increases with elevated MAP, 4) when AR is intact, or relatively strong, ICP

remains unchanged or decreases when BP is increased, 5) PbtO2 in most patients increased with elevation of MAP but the magnitude of this response was still related to ARI, and 6) an association between ARI and outcome was not demonstrated.

Methodological Limitations

There are several potential methodological limitations to this study. First, AR testing was not performed on every patient, and the time and frequency of testing was variable. Also, patients who died within the first 24 hours did not undergo AR testing, AR testing was not performed every day, and AR testing was not performed if patients were haemodynamically unstable or if there had been a rapid deterioration in ICP control. Therefore, the prevalence of impaired AR in this study may underestimate the true prevalence. Second, we cannot exclude the possibility that phenylephrine may have direct cerebrovascular effects. However, phenylephrine appears to have minimal direct effects on cerebral blood vessels [62, 181] and for this reason it is generally the preferred agent for AR testing (Chapter 5). Third, we cannot exclude that longer periods at higher BP may have other cerebrovascular consequences, such as increasing blood-brain permeability and vasogenic edema [102]. Fourth, we did not test AR across the full range of the autoregulatory plateau. Therefore, patients with apparent intact AR may have tested differently at different MAP intervals or over a larger range of MAP. However, AR testing was used in this study as a pragmatic guide to gain information about the intracranial dynamics in a range of elevated MAP that the individual patient may experience spontaneously or that clinicians may have used to improve PbtO2. Therefore, we cannot extrapolate these results to the full range of BP over which AR is expected to be active in healthy individuals. Despite these limitations, however, the results of this study confirm the association of impaired AR with low initial GCS, and demonstrate the inverse relationship between the strength of the AR and the change in ICP and PbtO2 with an increase in BP.

Autoregulation and Outcome

AR was not associated with outcome in this study. Several other studies, however, have demonstrated an association between impaired AR and poor outcome (Chapter 5). This may merely reflect the individual relationships that both impaired AR and poor outcome have with increased severity of injury. On the other hand, because the status of AR determines the cerebral hemodynamic

response to spontaneous and induced changes in BP, it is equally possible that impaired AR may directly worsen outcome by increasing the risk of secondary injury. For example, impaired AR may lead to cerebral ischaemia or cerebral congestion at unpredictable CPP levels. A possible explanation for the lack of relationship between impaired AR and outcome in the present study is that the timing of testing was variable and the most severely injured patients may not have been tested. However, this is probably true of many of the other studies that have shown a relationship between AR and outcome. An alternative explanation is that results from AR testing influenced management which may have confounded the association with outcome. Therefore, the possibility that appropriate responses to the status of AR may influence outcome warrants further study.

Response of ICP to Elevated BP

It is well recognized that BP changes have a variable effect on cerebrovascular volume depending on the status of AR. Rosner et al [300, 301] proposed that CPP be maintained at higher levels to actively manage ICP by avoiding the vasodilatory cascade associated with lower CPP when AR is intact, assuming that active cerebral arterioles vasoconstrict with increased BP, thereby reducing cerebral blood volume and ICP. However, if AR is impaired, this approach would increase CBF and cerebral blood volume, thereby increasing ICP. This increase of ICP when AR is impaired is demonstrated in the present study. However, in a small proportion of cases (9%) the response of ICP was unexpected, i.e. there was an increase in ICP even when AR was thought to be intact. There are a number of possible explanations for these cases. First, during the time required for AR testing there may have been spontaneous fluctuations in ICP unrelated to the test which may confound these results. Second, the distinction between impaired versus intact AR is not precise. The strength of AR is a continuum; therefore only an ARI of 0 implies completely absent AR. However, maximal ARI (ARI near or equal to 1) is expected in healthy individuals and reduced ARI is associated with decreasing autoregulatory capacity in head-injured individuals. Despite these limitations however, these results demonstrate the increased risk of worsening ICP when BP is increased in patients with impaired AR.

Response of PbtO2 to Elevated BP

Several studies have examined the relationship between CPP and PbtO2, and specifically the influence of CPP augmentation on PbtO2; however, the results have been conflicting (Chapter 6). In general, these studies do not clarify whether AR was intact or not, but cite AR as a reason for variability in the relationship between BP and PbtO2. Menzel et al [237] examined the relationship between spontaneous fluctuations in CPP and PbtO2 in patients with TBI and uninjured animals. PbtO2 changes were closely correlated with CPP changes in the head-injured patients but not in the uninjured animals, which the authors suggested was probably due to either global or local failure of AR in the head-injured patients. Few human studies have directly measured the relationship between AR and PbtO2. Jaeger et al [161] reported a close association between PbtO2 changes and the status of AR as determined by observation of the relationship between ICP and spontaneous fluctuations in BP in adult TBI. One study examined formally tested AR (with TCD) and the PbtO2 response to increased BP in 14 adult patients [187]. They found a plateau phase in the PbtO2 response in the region of 70-90 mmHg that correlated with the plateau phase of FV_{MCA}. The authors suggested that the PbtO2 response may be useful in the interpretation of AR. The finding in our study that PbtO2, although related to ARI, often increased despite FV_{MCA} results implying intact AR suggests that local regulatory mechanisms may be impaired even when global AR is intact. This local disturbance of regulatory mechanisms may be particularly prevalent in peri-contusional locations [272]. When ARI was ≥0.4 *and* ICP decreased or remained unchanged in response to increased BP, PbtO2 still increased in most cases (67%). Therefore, the PbtO2 response may reflect local mechanisms as much as it does hemispheral autoregulatory capacity.

ARI and Baseline Variables

AR has been reported to be more commonly impaired if baseline ICP is higher [80]. In the present study, ARI was not associated with baseline ICP, although it is possible that this may in part be influenced by the fact that ICP was usually <20mmHg at the time of testing. ICP was ≥20 mmHg at the time of testing in 21% of cases (11 of 52). However, mean ARI was similar in patients with and without ICP ≥ 20 mmHg (ARI 0.76 versus 0.76). Others have suggested an association between FV_{MCA} and impaired AR, and specifically that children who have hyperaemia (based on TCD) may have a higher incidence of impaired AR [397]. This relationship was not demonstrated in the present

study. Patients with $FV_{MCA} \geq 120$ cm/s had a mean ARI of 0.76 compared to an ARI of 0.77 in those with $FV_{MCA} < 120$ cm/s at the time of testing. The diagnosis of hyperaemia in children is not precise. Strictly it should only be diagnosed on the basis of measures of the relationship between CBF and metabolism. Therefore, TCD-derived absolute values of flow velocity may not be adequate to demonstrate a relationship between impaired AR and true hyperaemia.

Conclusion

In this study low initial GCS was associated with worse autoregulatory function in children with severe TBI. Impaired AR was associated with increased ICP when BP was increased. The PbtO2 response to increased BP was also related to the autoregulatory capacity but usually increased even when AR appeared to be intact, which may reflect impaired local tissue regulatory mechanisms. Formal testing of AR may assist clinical decision-making in paediatric TBI.

Thesis Summary and Conclusion

TBI remains a major challenge to neurosurgeons and neurointensivists managing patients in the acute setting. Clinicians treating children are faced with the additional challenge of treating a developing human. Research into pharmacological treatments for TBI has produced little to advance care of these patients. Therefore, the focus must be on better management of the patient to prevent secondary injury. However, there are considerable challenges. First, conventional management of severe TBI that combines clinical and radiographic assessment with ICP and CPP monitoring alone may miss important secondary insults and may not be optimal for understanding the pathophysiological disturbances in individual patients. Second, therapies that we have used in the past, and perhaps continue to use today, have harmed patients because we have been unable to prove their benefit or detect their adverse effects. Third, because all therapies have a risk/benefit ratio, specific treatments may be beneficial for some patients but not for others. This distinction may be determined by differences in the physiological responses to trauma between individuals.

This thesis has examined the potential benefits of the addition of PbtO2, TCD and autoregulation monitoring as bedside investigations in the ICU to 1) improve our understanding of complex pathophysiological processes occurring in the individual patient with TBI, and 2) improve our detection of secondary insults and subsequent management of the paediatric patient with severe TBI.

To accomplish these aims, the work 1) examined the information gained from these additional monitoring strategies, and 2) examined interactions between several measured variables and their relationships with outcome.

The body of the work consisted largely of a prospective observational study of 52 children with severe TBI and was divided into discrete parts, each of which aimed to address specific questions. The main findings were:

1) Episodes of low PbtO2 were surprisingly common after severe TBI. Most importantly, clinically important episodes (PbtO2<10mmHg) occurred often despite adherence to conventional treatment targets
2) Clinical and other physiological parameters have a variable overall relationship with episodes of low PbtO2; however, in individual patients, disturbances of normal physiology such as elevated ICP, may have an important adverse effect on PbtO2 that responds to treatment
3) Low PbtO2 is an independent predictor of poor clinical outcome after TBI and delayed brain infarction, particularly when of long duration
4) Acute admission grading systems used for prognostication in paediatric TBI do not necessarily predict who is at risk for secondary injury
5) PbtO2 monitoring is one modality that can be used to assess the influence of therapies on intracranial dynamics. As an example, the effects of blood transfusion on PbtO2 were evaluated. Although PbtO2 was increased in the majority of patients, the effects were small, variable, and not easily predicted by pre-transfusion factors. This is important because of the risk/benefit ratio of the therapy.

6) TCD-monitored MCA flow velocities have associations with ICP and PbtO2, but are probably best interpreted in individual patients in combination with other factors. The range in MCA flow velocities was wide (32-180cm/s) which emphasizes the major differences between individual patients. Vasospasm in paediatric TBI appears to be uncommon.
7) TCD-derived PI does not correlate with ICP in paediatric TBI; however, low CPP correlates with a rise in the PI and may have a role in CPP estimation when ICP monitoring has not yet been instituted.
8) Bedside determination of autoregulation with TCD is feasible in children with TBI. Impaired autoregulation is associated with low admission GCS, and results in increased ICP when BP is increased. This may be important information when determining the effects of CPP manipulation and optimal CPP. PbtO2 responses to BP increases likely depend not only on the global status of autoregulation but also on local microvascular factors.
9) Induced normobaric hyperoxia increases PbtO2 reliably; however, the magnitude of the response varies widely, and is best related to the baseline PbtO2. The clinical benefits of this are an important issue that needs further testing.
10) The ratio of increase in PbtO2 to the increase in PaO2 has an inverse relationship with outcome. This may imply failure of local O2 regulatory mechanism in injured tissue.

In conclusion, this work highlights the complexity and heterogeneity of severe TBI and suggests that conventional approaches to monitoring may miss clinically important secondary brain insults that lead to poor outcome. Data from practical bedside methods, such as PbtO2 and TCD monitoring, complement ICP and CPP monitoring by improving detection of potential brain insults and monitoring the effects of various therapies in the ICU. They contribute to our understanding of complex pathophysiological interactions in the head-injured child and may lead to improved outcomes by individualising treatment and directing appropriate therapy. The combination of the

observed variations in PbtO2, ICP, flow velocities, and strength of autoregulatory capacity in this study would seem to argue strongly that treatment should be individualised to the patient. With the addition of these, and other new technologies and novel strategies for monitoring in the future, we may begin to better appreciate the complexity of secondary injury avoidance and the adverse effects of our therapies. Important lessons have been learned in the past of our failure to appreciate secondary insults and of well-intentioned treatments that have had negative consequences for the patient. It is hoped that better understanding will help further tailor therapy to individual patients to give them the best chance of a favourable outcome.

Anthony A. Figaji, 15 August 2008

References

1. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H: Cerebral autoregulation dynamics in humans. **Stroke 20:**45-52, 1989

2. Aaslid R, Markwalder TM, Nornes H: Noninvasive transcranial doppler ultrasound recording of flow velocity in basal cerebral arteries. **J Neurosurg 57:**769-774, 1982

3. Adelson PD, Bratton SL, Carney NA, Chesnut RM, du Coudray HE, Goldstein B, et al: Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 4. Resuscitation of blood pressure and oxygenation and prehospital brain-specific therapies for the severe pediatric traumatic brain injury patient. **Pediatr Crit Care Med 4:**S12-8, 2003

4. Adelson PD, Bratton SL, Carney NA, Chesnut RM, du Coudray HE, Goldstein B, et al: Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 1: Introduction. **Pediatr Crit Care Med 4:**S2-4, 2003

5. Adelson PD, Bratton SL, Carney NA, Chesnut RM, du Coudray HE, Goldstein B, et al: Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 12. Use of hyperventilation in the acute management of severe pediatric traumatic brain injury. **Pediatr Crit Care Med 4:**S45-8, 2003

6. Adelson PD, Bratton SL, Carney NA, Chesnut RM, du Coudray HE, Goldstein B, et al: Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 5. Indications for intracranial pressure monitoring in pediatric patients with severe traumatic brain injury. **Pediatr Crit Care Med 4:**S19-24, 2003

7. Adelson PD, Bratton SL, Carney NA, Chesnut RM, du Coudray HE, Goldstein B, et al: Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and

adolescents. Chapter 6. Threshold for treatment of intracranial hypertension. **Pediatr Crit Care Med 4:**S25-7, 2003

8. Adelson PD, Bratton SL, Carney NA, Chesnut RM, du Coudray HE, Goldstein B, et al: Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 8. Cerebral perfusion pressure. **Pediatr Crit Care Med 4:**S31-3, 2003

9. Adelson PD, Bratton SL, Carney NA, Chesnut RM, du Coudray HE, Goldstein B, et al: Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 9. Use of sedation and neuromuscular blockade in the treatment of severe pediatric traumatic brain injury. **Pediatr Crit Care Med 4:**S34-7, 2003

10. Adelson PD, Clyde B, Kochanek PM, Wisniewski SR, Marion DW, Yonas H: Cerebrovascular response in infants and young children following severe traumatic brain injury: A preliminary report. **Pediatr Neurosurg 26:**200-207, 1997

11. Adelson PD, Nemoto E, Colak A, Painter M: The use of near infrared spectroscopy (NIRS) in children after traumatic brain injury: A preliminary report. **Acta Neurochir Suppl 71:**250-254, 1998

12. Akopian G, Gaspard DJ, Alexander M: Outcomes of blunt head trauma without intracranial pressure monitoring. **Am Surg 73:**447-450, 2007

13. Aldrich EF, Eisenberg HM, Saydjari C, Luerssen TG, Foulkes MA, Jane JA, et al: Diffuse brain swelling in severely head-injured children. A report from the NIH traumatic coma data bank. **J Neurosurg 76:**450-454, 1992

14. Al-Rawi PG, Hutchinson PJ, Gupta AK, Piechnik SK, Pickard JD, Kirkpatrick PJ: Multiparameter brain tissue monitoring--correlation between parameters and identification of CPP thresholds. **Zentralbl Neurochir 61:**74-79, 2000

15. Al-Rawi PG, Kirkpatrick PJ: Tissue oxygen index: Thresholds for cerebral ischemia using near-infrared spectroscopy. **Stroke 37:**2720-2725, 2006

16. Al-Rawi PG, Smielewski P, Kirkpatrick PJ: Evaluation of a near-infrared spectrometer (NIRO 300) for the detection of intracranial oxygenation changes in the adult head. **Stroke 32:**2492-2500, 2001

17. Ananda A, Morris GF, Juul N, Marshall SB, Marshall LF: The frequency, antecedent events, and causal relationships of neurologic worsening following severe head injury. executive committee of the international selfotel trial. **Acta Neurochir Suppl 73:**99-102, 1999

18. Anderson V, Catroppa C, Morse S, Haritou F, Rosenfeld J: Functional plasticity or vulnerability after early brain injury? **Pediatrics 116:**1374-1382, 2005

19. Andrews PJ, Citerio G: Lund therapy - pathophysiology-based therapy or contrived over-interpretation of limited data? **Intensive Care Med 32:**1461-1463, 2006

20. Arias E, Anderson RN, Kung HC, Murphy SL, Kochanek KD: Deaths: Final data for 2001. **National Vital Statistics Reports 52(3):**1-116, 2003

21. Armano R, Gauvin F, Ducruet T, Lacroix J: Determinants of red blood cell transfusions in a pediatric critical care unit: A prospective, descriptive epidemiological study. **Crit Care Med 33:**2637-2644, 2005

22. Asgeirsson B, Grande PO, Nordstrom CH: A new therapy of post-trauma brain oedema based on haemodynamic principles for brain volume regulation. **Intensive Care Med 20:**260-267, 1994

23. Astrup J, Siesjo BK, Symon L: Thresholds in cerebral ischemia - the ischemic penumbra. **Stroke 12:**723-725, 1981

24. Balestreri M, Czosnyka M, Chatfield DA, Steiner LA, Schmidt EA, Smielewski P, et al: Predictive value of glasgow coma scale after brain trauma: Change in trend over the past ten years. **J Neurol Neurosurg Psychiatry 75:**161-162, 2004

25. Bandres J, Yao L, Nemoto EM, Yonas H, Darby J: Effects of dobutamine and dopamine on whole brain blood flow and metabolism in unanesthetized monkeys. **J Neurosurg Anesthesiol 4:**250-256, 1992

26. Bardt TF, Unterberg AW, Hartl R, Kiening KL, Schneider GH, Lanksch WR: Monitoring of brain tissue PO2 in traumatic brain injury: Effect of cerebral hypoxia on outcome. **Acta Neurochir Suppl 71:**153-156, 1998

27. Baumgartl H, Zimelka W, Lubbers DW: Evaluation of PO(2) profiles to describe the oxygen pressure field within the tissue. **Comp Biochem Physiol A Mol Integr Physiol 132:**75-85, 2002

28. Bellander BM, Cantais E, Enblad P, Hutchinson P, Nordstrom CH, Robertson C, et al: Consensus meeting on microdialysis in neurointensive care. **Intensive Care Med 30:**2166-2169, 2004

29. Bellner J, Romner B, Reinstrup P, Kristiansson KA, Ryding E, Brandt L: Transcranial doppler sonography pulsatility index (PI) reflects intracranial pressure (ICP). **Surg Neurol 62:**45-51; discussion 51, 2004

30. Berger S, Schwarz M, Huth R: Hypertonic saline solution and decompressive craniectomy for treatment of intracranial hypertension in pediatric severe traumatic brain injury. **J Trauma 53:**558-563, 2002

31. Bhatia A, Gupta AK: Neuromonitoring in the intensive care unit. II. cerebral oxygenation monitoring and microdialysis. **Intensive Care Med 33:**1322-1328, 2007

32. Bishop CC, Powell S, Rutt D, Browse NL: Transcranial doppler measurement of middle cerebral artery blood flow velocity: A validation study. **Stroke 17:**913-915, 1986

33. Bouma GJ, Muizelaar JP: Relationship between cardiac output and cerebral blood flow in patients with intact and with impaired autoregulation. **J Neurosurg 73:**368-374, 1990

34. Bouma GJ, Muizelaar JP, Bandoh K, Marmarou A: Blood pressure and intracranial pressure-volume dynamics in severe head injury: Relationship with cerebral blood flow. **J Neurosurg 77:**15-19, 1992

35. Bouma GJ, Muizelaar JP, Choi SC, Newlon PG, Young HF: Cerebral circulation and metabolism after severe traumatic brain injury: The elusive role of ischemia. **J Neurosurg 75:**685-693, 1991

36. Bouma GJ, Muizelaar JP, Stringer WA, Choi SC, Fatouros P, Young HF: Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. **J Neurosurg 77:**360-368, 1992

37. Bowman SM, Martin DP, Sharar SR, Zimmerman FJ: Racial disparities in outcomes of persons with moderate to severe traumatic brain injury. **Med Care 45:**686-690, 2007

38. Bradshaw D, Bourne D, Nannan N: What are the leading causes of death among South African children? **South African Medical Research Council Policy Brief 3:**2003

39. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS, Bratton SL, Chestnut RM, et al: Guidelines for the management of severe traumatic brain injury. IX. Cerebral perfusion thresholds. **J Neurotrauma 24 Suppl 1:**S59-64, 2007

40. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS, Bratton SL, Chestnut RM, et al: Guidelines for the management of severe traumatic brain injury. VI. Indications for intracranial pressure monitoring. **J Neurotrauma 24 Suppl 1:**S37-44, 2007

41. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS, Bratton SL, Chestnut RM, et al: Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds. **J Neurotrauma 24 Suppl 1:**S55-8, 2007

42. Bruce DA, Alavi A, Bilaniuk L, Dolinskas C, Obrist W, Uzzell B: Diffuse cerebral swelling following head injuries in children: The syndrome of "malignant brain edema". **J Neurosurg 54:**170-178, 1981

43. Bruce DA, Raphaely RC, Goldberg AI, Zimmerman RA, Bilaniuk LT, Schut L, et al: Pathophysiology, treatment and outcome following severe head injury in children. **Childs Brain 5:**174-191, 1979

44. Bruce DA, Schut L, Bruno LA, Wood JH, Sutton LN: Outcome following severe head injuries in children. **J Neurosurg 48:**679-688, 1978

45. Bruzzone P, Dionigi R, Bellinzona G, Imberti R, Stocchetti N: Effects of cerebral perfusion pressure on brain tissue PO2 in patients with severe head injury. **Acta Neurochir Suppl 71**:111-113, 1998

46. Buchner K, Meixensberger J, Dings J, Roosen K: Near-infrared spectroscopy - not useful to monitor cerebral oxygenation after severe brain injury. **Zentralbl Neurochir 61**:69-73, 2000

47. Bullock MR: Hyperoxia: Good or bad? **J Neurosurg 98**:943-4, 2003

48. Bullock MR, Chesnut R, Ghajar J, Gordon D, Hartl R, Newell DW, et al: Surgical management of traumatic parenchymal lesions. **Neurosurgery 58**:S25-46, 2006

49. Busija DW, Orr JA, Rankin JH, Liang HK, Wagerle LC: Cerebral blood flow during normocapnic hyperoxia in the unanesthetized pony. **J Appl Physiol 48**:10-15, 1980

50. Cantais E, Paut O, Giorgi R, Viard L, Camboulives J: Evaluating the prognosis of multiple, severely traumatized children in the intensive care unit. **Intensive Care Med 27**:1511-1517, 2001

51. Carli P, Orliaguet G: Severe traumatic brain injury in children. **Lancet 363**:584-585, 2004

52. Carson JL, Duff A, Poses RM, Berlin JA, Spence RK, Trout R, et al: Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. **Lancet 348**:1055-1060, 1996

53. Casutt M, Seifert B, Pasch T, Schmid ER, Turina MI, Spahn DR: Factors influencing the individual effects of blood transfusions on oxygen delivery and oxygen consumption. **Crit Care Med 27**:2194-2200, 1999

54. Catala-Temprano A, Claret Teruel G, Cambra Lasaosa FJ, Pons Odena M, Noguera Julian A, Palomeque Rico A: Intracranial pressure and cerebral perfusion pressure as risk factors in children with traumatic brain injuries. **J Neurosurg 106**:463-466, 2007

55. Center for Disease Control: Web-based injury statistics query and reporting system (WISQARS). **Online at http://www.cdc.gov/ncipc/wisqars/** Accessed 15 May 2008.

56. Chambers IR, Jones PA, Lo TY, Forsyth RJ, Fulton B, Andrews PJ, et al: Critical thresholds of intracranial pressure and cerebral perfusion pressure related to age in paediatric head injury. **J Neurol Neurosurg Psychiatry 77:**234-240, 2006

57. Chambers IR, Treadwell L, Mendelow AD: The cause and incidence of secondary insults in severely head-injured adults and children. **Br J Neurosurg 14:**424-431, 2000

58. Chambers IR, Treadwell L, Mendelow AD: Determination of threshold levels of cerebral perfusion pressure and intracranial pressure in severe head injury by using receiver-operating characteristic curves: An observational study in 291 patients. **J Neurosurg 94:**412-416, 2001

59. Chan KH, Dearden NM, Miller JD: The significance of posttraumatic increase in cerebral blood flow velocity: A transcranial doppler ultrasound study. **Neurosurgery 30:**697-700, 1992

60. Chan KH, Miller JD, Dearden NM, Andrews PJ, Midgley S: The effect of changes in cerebral perfusion pressure upon middle cerebral artery blood flow velocity and jugular bulb venous oxygen saturation after severe brain injury. **J Neurosurg 77:**55-61, 1992

61. Chang CJ, Chang WN, Huang LT, Chang YC, Huang SC, Hung PL, et al: Cerebral infarction in perinatal and childhood bacterial meningitis. **QJM 96:**755-762, 2003

62. Cherian L, Chacko G, Goodman JC, Robertson CS: Cerebral hemodynamic effects of phenylephrine and L-arginine after cortical impact injury. **Crit Care Med 27:**2512-2517, 1999

63. Chesnut RM: Re: Intracranial pressure monitoring in brain-injured patients is associated with worsening of survival. **J Trauma 65:**500-501, 2008

64. Chesnut RM, Marshall LF, Klauber MR, Blunt BA, Baldwin N, Eisenberg HM, et al: The role of secondary brain injury in determining outcome from severe head injury. **J Trauma 34:**216-222, 1993

65. Chiaretti A, De Benedictis R, Della Corte F, Piastra M, Viola L, Polidori G, et al: The impact of initial management on the outcome of children with severe head injury. **Childs Nerv Syst 18:**54-60, 2002

66. Chiaretti A, Piastra M, Pulitano S, Pietrini D, De Rosa G, Barbaro R, et al: Prognostic factors and outcome of children with severe head injury: An 8-year experience. **Childs Nerv Syst 18:**129-136, 2002

67. Chieregato A, Calzolari F, Trasforini G, Targa L, Latronico N: Normal jugular bulb oxygen saturation. **J Neurol Neurosurg Psychiatry 74:**784-786, 2003

68. Chin-Yee I, Arya N, d'Almeida MS: The red cell storage lesion and its implication for transfusion. **Transfus Sci 18:**447-458, 1997

69. Chiron C, Raynaud C, Maziere B, Zilbovicius M, Laflamme L, Masure MC, et al: Changes in regional cerebral blood flow during brain maturation in children and adolescents. **J Nucl Med 33:**696-703, 1992

70. Clausen T, Khaldi A, Zauner A, Reinert M, Doppenberg E, Menzel M, et al: Cerebral acid-base homeostasis after severe traumatic brain injury. **J Neurosurg 103:**597-607, 2005

71. Coates BM, Vavilala MS, Mack CD, Muangman S, Suz P, Sharar SR, et al: Influence of definition and location of hypotension on outcome following severe pediatric traumatic brain injury. **Crit Care Med 33:**2645-2650, 2005

72. Cohen PJ, Alexander SC, Smith TC, Reivich M, Wollman H: Effects of hypoxia and normocarbia on cerebral blood flow and metabolism in conscious man. **J Appl Physiol 23:**183-189, 1967

73. Coles JP, Fryer TD, Coleman MR, Smielewski P, Gupta AK, Minhas PS, et al: Hyperventilation following head injury: Effect on ischemic burden and cerebral oxidative metabolism. **Crit Care Med 35:**568-578, 2007

74. Coles JP, Fryer TD, Smielewski P, Chatfield DA, Steiner LA, Johnston AJ, et al: Incidence and mechanisms of cerebral ischemia in early clinical head injury. **J Cereb Blood Flow Metab 24:**202-211, 2004

75. Coles JP, Fryer TD, Smielewski P, Rice K, Clark JC, Pickard JD, et al: Defining ischemic burden after traumatic brain injury using 15O PET imaging of cerebral physiology. **J Cereb Blood Flow Metab 24**:191-201, 2004

76. Coles JP, Steiner LA, Johnston AJ, Fryer TD, Coleman MR, Smieleweski P, et al: Does induced hypertension reduce cerebral ischaemia within the traumatized human brain? **Brain 127**:2479-2490, 2004

77. Cormio M, Valadka AB, Robertson CS: Elevated jugular venous oxygen saturation after severe head injury. **J Neurosurg 90**:9-15, 1999

78. Corwin HL, Surgenor SD, Gettinger A: Transfusion practice in the critically ill. **Crit Care Med 31**:S668-71, 2003

79. Cremer OL: Does ICP monitoring make a difference in neurocritical care? **Eur J Anaesthesiol Suppl 42**:87-93, 2008

80. Cremer OL, van Dijk GW, Amelink GJ, de Smet AM, Moons KG, Kalkman CJ: Cerebral hemodynamic responses to blood pressure manipulation in severely head-injured patients in the presence or absence of intracranial hypertension. **Anesth Analg 99**:1211-7, 2004

81. Cremer OL, van Dijk GW, van Wensen E, Brekelmans GJ, Moons KG, Leenen LP, et al: Effect of intracranial pressure monitoring and targeted intensive care on functional outcome after severe head injury. **Crit Care Med 33**:2207-2213, 2005

82. Cunningham AS, Salvador R, Coles JP, Chatfield DA, Bradley PG, Johnston AJ, et al: Physiological thresholds for irreversible tissue damage in contusional regions following traumatic brain injury. **Brain 128**:1931-1942, 2005

83. Czosnyka M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD: Monitoring of cerebral autoregulation in head-injured patients. **Stroke 27**:1829-1834, 1996

84. Czosnyka M, Smielewski P, Lavinio A, Pickard JD, Panerai R: An assessment of dynamic autoregulation from spontaneous fluctuations of cerebral blood flow velocity: A comparison of two models, index of autoregulation and mean flow index. **Anesth Analg 106:**234-9, 2008

85. Czosnyka M, Smielewski P, Piechnik S, Steiner LA, Pickard JD: Cerebral autoregulation following head injury. **J Neurosurg 95:**756-763, 2001

86. de Villiers JC, Jacobs M, Parry CD, Botha JL: A retrospective study of head-injured children admitted to two hospitals in Cape Town. **S Afr Med J 66:**801-805, 1984

87. Dean NP, Boslaugh S, Adelson PD, Pineda JA, Leonard JR: Physician agreement with evidence-based recommendations for the treatment of severe traumatic brain injury in children. **J Neurosurg 107:**387-391, 2007

88. Dearden NM, Midgley S: Technical considerations in continuous jugular venous oxygen saturation measurement. **Acta Neurochir Suppl (Wien) 59:**91-97, 1993

89. Dings J, Meixensberger J, Amschler J, Hamelbeck B, Roosen K: Brain tissue pO2 in relation to cerebral perfusion pressure, TCD findings and TCD-CO2-reactivity after severe head injury. **Acta Neurochir (Wien) 138:**425-434, 1996

90. Dings J, Meixensberger J, Jager A, Roosen K: Clinical experience with 118 brain tissue oxygen partial pressure catheter probes. **Neurosurgery 43:**1082-1095, 1998

91. Diringer MN, Aiyagari V, Zazulia AR, Videen TO, Powers WJ: Effect of hyperoxia on cerebral metabolic rate for oxygen measured using positron emission tomography in patients with acute severe head injury. **J Neurosurg 106:**526-529, 2007

92. Diringer MN, Videen TO, Yundt K, Zazulia AR, Aiyagari V, Dacey RG,Jr, et al: Regional cerebrovascular and metabolic effects of hyperventilation after severe traumatic brain injury. **J Neurosurg 96:**103-108, 2002

93. Diringer MN, Yundt K, Videen TO, Adams RE, Zazulia AR, Deibert E, et al: No reduction in cerebral metabolism as a result of early moderate hyperventilation following severe traumatic brain injury. **J Neurosurg 92:**7-13, 2000

94. Doppenberg EM, Rice MR, Di X, Young HF, Woodward JJ, Bullock R: Increased free radical production due to subdural hematoma in the rat: Effect of increased inspired oxygen fraction. **J Neurotrauma 15:**337-347, 1998

95. Doppenberg EM, Watson JC, Broaddus WC, Holloway KL, Young HF, Bullock R: Intraoperative monitoring of substrate delivery during aneurysm and hematoma surgery: Initial experience in 16 patients. **J Neurosurg 87:**809-816, 1997

96. Doppenberg EM, Zauner A, Bullock R, Ward JD, Fatouros PP, Young HF: Correlations between brain tissue oxygen tension, carbon dioxide tension, pH, and cerebral blood flow - a better way of monitoring the severely injured brain? **Surg Neurol 49:**650-654, 1998

97. Doppenberg EM, Zauner A, Watson JC, Bullock R: Determination of the ischemic threshold for brain oxygen tension. **Acta Neurochir Suppl 71:**166-169, 1998

98. Downard C, Hulka F, Mullins RJ, Piatt J, Chesnut R, Quint P, et al: Relationship of cerebral perfusion pressure and survival in pediatric brain-injured patients. **J Trauma 49:**654-8, 2000

99. Ducrocq SC, Meyer PG, Orliaguet GA, Blanot S, Laurent-Vannier A, Renier D, et al: Epidemiology and early predictive factors of mortality and outcome in children with traumatic severe brain injury: Experience of a French pediatric trauma center. **Pediatr Crit Care Med 7:**461-467, 2006

100. Dudkiewicz M, Proctor KG: Tissue oxygenation during management of cerebral perfusion pressure with phenylephrine or vasopressin. **Crit Care Med:** Aug 1, Epub Ahead of Print, 2008

101. Duhaime AC, Christian CW, Rorke LB, Zimmerman RA: Nonaccidental head injury in infants - the "shaken-baby syndrome". **N Engl J Med 338:**1822-1829, 1998

102. Durward QJ, Del Maestro RF, Amacher AL, Farrar JK: The influence of systemic arterial pressure and intracranial pressure on the development of cerebral vasogenic edema. **J Neurosurg 59:**803-809, 1983

103. Edvinsson L, Lacombe P, Owman C, Reynier-Rebuffel AM, Seylaz J: Quantitative changes in regional cerebral blood flow of rats induced by alpha- and beta-adrenergic stimulants. **Acta Physiol Scand 107:**289-296, 1979

104. Eker C, Asgeirsson B, Grande PO, Schalen W, Nordstrom CH: Improved outcome after severe head injury with a new therapy based on principles for brain volume regulation and preserved microcirculation. **Crit Care Med 26:**1881-1886, 1998

105. Elf K, Nilsson P, Enblad P: Outcome after traumatic brain injury improved by an organized secondary insult program and standardized neurointensive care. **Crit Care Med 30:**2129-2134, 2002

106. Ellsworth ML: The red blood cell as an oxygen sensor: What is the evidence? **Acta Physiol Scand 168:**551-559, 2000

107. Farrell LS, Hannan EL, Cooper A: Severity of injury and mortality associated with pediatric blunt injuries: Hospitals with pediatric intensive care units versus other hospitals. **Pediatr Crit Care Med 5:**5-9, 2004

108. Fearing MA, Bigler ED, Wilde EA, Johnson JL, Hunter JV, Xiaoqi L, et al: Morphometric MRI findings in the thalamus and brainstem in children after moderate to severe traumatic brain injury. **J Child Neurol 23:**729-737, 2008

109. Feickert HJ, Drommer S, Heyer R: Severe head injury in children: Impact of risk factors on outcome. **J Trauma 47:**33-38, 1999

110. Figaji AA, Fieggen AG, Argent A, Peter JC: Surgical treatment for "brain compartment syndrome" in children with severe head injury. **S Afr Med J 96:**969-975, 2006

111. Figaji AA, Fieggen AG, Peter JC: Early decompressive craniotomy in children with severe traumatic brain injury. **Childs Nerv Syst 19:**666-673, 2003

112. Figaji AA, Fieggen AG, Peter JC: Endoscopy for tuberculous hydrocephalus. **Childs Nerv Syst 23:**79-84, 2007

113. Figaji AA, Sandler SJ, Fieggen AG, Le Roux PD, Peter JC, Argent AC: Continuous monitoring and intervention for cerebral ischemia in tuberculous meningitis. **Pediatr Crit Care Med 9:**e25-e30, 2008

114. Fiser DH: Assessing the outcome of pediatric intensive care. **J Pediatr 121:**68-74, 1992

115. Fiser DH, Long N, Roberson PK, Hefley G, Zolten K, Brodie-Fowler M: Relationship of pediatric overall performance category and pediatric cerebral performance category scores at pediatric intensive care unit discharge with outcome measures collected at hospital discharge and 1- and 6-month follow-up assessments. **Crit Care Med 28:**2616-2620, 2000

116. Fitzgerald RD, Martin CM, Dietz GE, Doig GS, Potter RF, Sibbald WJ: Transfusing red blood cells stored in citrate phosphate dextrose adenine-1 for 28 days fails to improve tissue oxygenation in rats. **Crit Care Med 25:**726-732, 1997

117. Floyd TF, Clark JM, Gelfand R, Detre JA, Ratcliffe S, Guvakov D, et al: Independent cerebral vasoconstrictive effects of hyperoxia and accompanying arterial hypocapnia at 1 ATA. **J Appl Physiol 95:**2453-2461, 2003

118. Fog M: The relationship between the blood pressure and the tonic regulation of the pial arteries. **J Neurol Psychiatry 1:**187-197, 1938

119. Forsyth RJ, Parslow RC, Tasker RC, Hawley CA, Morris KP, UK Paediatric Traumatic Brain Injury Study Group, et al: Prediction of raised intracranial pressure complicating severe traumatic brain injury in children: Implications for trial design. **Pediatr Crit Care Med 9:**8-14, 2008

120. Freeman SS, Udomphorn Y, Armstead WM, Fisk DM, Vavilala MS: Young age as a risk factor for impaired cerebral autoregulation after moderate to severe pediatric traumatic brain injury. **Anesthesiology 108:**588-595, 2008

121. Gatto R, Hoffman W, Mueller M, Flores A, Valyi-Nagy T, Charbel FT: Frequency domain near-infrared spectroscopy technique in the assessment of brain oxygenation: A validation study in live subjects and cadavers. **J Neurosci Methods 157:**274-277, 2006

122. Giza CC, Mink RB, Madikians A: Pediatric traumatic brain injury: Not just little adults. **Curr Opin Crit Care 13:**143-152, 2007

123. Giza CC, Prins ML: Is being plastic fantastic? Mechanisms of altered plasticity after developmental traumatic brain injury. **Dev Neurosci 28:**364-379, 2006

124. Gonzalez AM, Yazici I, Kusza K, Siemionow M: Effects of fresh versus banked blood transfusions on microcirculatory hemodynamics and tissue oxygenation in the rat cremaster model. **Surgery 141:**630-639, 2007

125. Gopinath SP, Valadka AB, Uzura M, Robertson CS: Comparison of jugular venous oxygen saturation and brain tissue PO2 as monitors of cerebral ischemia after head injury. **Crit Care Med 27:**2337-2345, 1999

126. Gosling RG, King DH: Arterial assessment by doppler-shift ultrasound. **Proc R Soc Med 67:**447-449, 1974

127. Graham DI, Adams JH, Doyle D: Ischaemic brain damage in fatal non-missile head injuries. **J Neurol Sci 39:**213-234, 1978

128. Graham DI, Ford I, Adams JH, Doyle D, Teasdale GM, Lawrence AE, et al: Ischaemic brain damage is still common in fatal non-missile head injury. **J Neurol Neurosurg Psychiatry 52:**346-350, 1989

129. Grande PO: The "Lund concept" for the treatment of severe head trauma--physiological principles and clinical application. **Intensive Care Med 32:**1475-1484, 2006

130. Grinkeviciute DE, Kevalas R, Saferis V, Matukevicius A, Ragaisis V, Tamasauskas A: Predictive value of scoring system in severe pediatric head injury. **Medicina (Kaunas) 43:**861-869, 2007

131. Gupta AK, Hutchinson PJ, Al-Rawi P, Gupta S, Swart M, Kirkpatrick PJ, et al: Measuring brain tissue oxygenation compared with jugular venous oxygen saturation for monitoring cerebral oxygenation after traumatic brain injury. **Anesth Analg 88:**549-553, 1999

132. Gupta AK, Hutchinson PJ, Fryer T, Al-Rawi PG, Parry DA, Minhas PS, et al: Measurement of brain tissue oxygenation performed using positron emission tomography scanning to validate a novel monitoring method. **J Neurosurg 96:**263-268, 2002

133. Habler OP, Kleen MS, Hutter JW, Podtschaske AH, Tiede M, Kemming GI, et al: Effects of hyperoxic ventilation on hemodilution-induced changes in anesthetized dogs. **Transfusion 38:**135-144, 1998

134. Hackbarth RM, Rzeszutko KM, Sturm G, Donders J, Kuldanek AS, Sanfilippo DJ: Survival and functional outcome in pediatric traumatic brain injury: A retrospective review and analysis of predictive factors. **Crit Care Med 30:**1630-1635, 2002

135. Hahn YS, McLone DG: Risk factors in the outcome of children with minor head injury. **Pediatr Neurosurg 19:**135-142, 1993

136. Haque IU, Zaritsky AL: Analysis of the evidence for the lower limit of systolic and mean arterial pressure in children. **Pediatr Crit Care Med 8:**138-144, 2007

137. Hare GM, Mazer CD, Hutchison JS, McLaren AT, Liu E, Rassouli A, et al: Severe hemodilutional anemia increases cerebral tissue injury following acute neurotrauma. **J Appl Physiol 103:**1021-1029, 2007

138. Hartman M, Watson RS, Linde-Zwirble W, Clermont G, Lave J, Weissfeld L, et al: Pediatric traumatic brain injury is inconsistently regionalized in the united states. **Pediatrics 122:**e172-80, 2008

139. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, et al: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. transfusion requirements in critical care investigators, Canadian critical care trials group. **N Engl J Med 340:**409-417, 1999

140. Hebert PC, Yetisir E, Martin C, Blajchman MA, Wells G, Marshall J, et al: Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? **Crit Care Med 29:**227-234, 2001

141. Hemphill JC,3rd, Knudson MM, Derugin N, Morabito D, Manley GT: Carbon dioxide reactivity and pressure autoregulation of brain tissue oxygen. **Neurosurgery 48:**377-83, 2001

142. Hemphill JC,3rd, Smith WS, Sonne DC, Morabito D, Manley GT: Relationship between brain tissue oxygen tension and CT perfusion: Feasibility and initial results. **AJNR Am J Neuroradiol 26:**1095-1100, 2005

143. Hessen E, Anderson V, Nestvold K: MMPI-2 profiles 23 years after paediatric mild traumatic brain injury. **Brain Inj 22:**39-50, 2008

144. Hiler M, Czosnyka M, Hutchinson P, Balestreri M, Smielewski P, Matta B, et al: Predictive value of initial computerized tomography scan, intracranial pressure, and state of autoregulation in patients with traumatic brain injury. **J Neurosurg 104:**731-737, 2006

145. Hlatky R, Furuya Y, Valadka AB, Gonzalez J, Chacko A, Mizutani Y, et al: Dynamic autoregulatory response after severe head injury. **J Neurosurg 97:**1054-1061, 2002

146. Hlatky R, Valadka AB, Goodman JC, Contant CF, Robertson CS: Patterns of energy substrates during ischemia measured in the brain by microdialysis. **J Neurotrauma 21:**894-906, 2004

147. Hlatky R, Valadka AB, Gopinath SP, Robertson CS: Brain tissue oxygen tension response to induced hyperoxia reduced in hypoperfused brain. **J Neurosurg 108:**53-58, 2008

148. Hlatky R, Valadka AB, Robertson CS: Analysis of dynamic autoregulation assessed by the cuff deflation method. **Neurocrit Care 4:**127-132, 2006

149. Hlatky R, Valadka AB, Robertson CS: Intracranial pressure response to induced hypertension: Role of dynamic pressure autoregulation. **Neurosurgery 57:**917-23, 2005

150. Hoelper BM, Alessandri B, Heimann A, Behr R, Kempski O: Brain oxygen monitoring: In-vitro accuracy, long-term drift and response-time of Licox- and Neurotrend sensors. **Acta Neurochir (Wien) 147:**767-74, 2005

151. Hoffman WE, Charbel FT, Gonzalez-Portillo G, Ausman JI: Measurement of ischemia by changes in tissue oxygen, carbon dioxide, and pH. **Surg Neurol 51**:654-658, 1999

152. Holliday PO,3rd, Kelly DL,Jr, Ball M: Normal computed tomograms in acute head injury: Correlation of intracranial pressure, ventricular size, and outcome. **Neurosurgery 10**:25-28, 1982

153. Holzschuh M, Woertgen C, Metz C, Brawanski A: Dynamic changes of cerebral oxygenation measured by brain tissue oxygen pressure and near infrared spectroscopy. **Neurol Res 19**:246-248, 1997

154. Homburg AM, Jakobsen M, Enevoldsen E: Transcranial doppler recordings in raised intracranial pressure. **Acta Neurol Scand 87**:488-493, 1993

155. Howells T, Elf K, Jones PA, Ronne-Engstrom E, Piper I, Nilsson P, et al: Pressure reactivity as a guide in the treatment of cerebral perfusion pressure in patients with brain trauma. **J Neurosurg 102**:311-317, 2005

156. Huchzermeyer C, Albus K, Gabriel HJ, Otahal J, Taubenberger N, Heinemann U, et al: Gamma oscillations and spontaneous network activity in the hippocampus are highly sensitive to decreases in pO2 and concomitant changes in mitochondrial redox state. **J Neurosci 28**:1153-1162, 2008

157. Hukkelhoven CW, Steyerberg EW, Rampen AJ, Farace E, Habbema JD, Marshall LF, et al: Patient age and outcome following severe traumatic brain injury: An analysis of 5600 patients. **J Neurosurg 99**:666-673, 2003

158. Hutchinson PJ, Gupta AK, Fryer TF, Al-Rawi PG, Chatfield DA, Coles JP, et al: Correlation between cerebral blood flow, substrate delivery, and metabolism in head injury: A combined microdialysis and triple oxygen positron emission tomography study. **J Cereb Blood Flow Metab 22**:735-745, 2002

159. Hutchison JS, Ward RE, Lacroix J, Hebert PC, Barnes MA, Bohn DJ, et al: Hypothermia therapy after traumatic brain injury in children. **N Engl J Med 358**:2447-2456, 2008

160. Imberti R, Bellinzona G, Langer M: Cerebral tissue PO2 and SjvO2 changes during moderate hyperventilation in patients with severe traumatic brain injury. **J Neurosurg 96:**97-102, 2002

161. Jaeger M, Schuhmann MU, Soehle M, Meixensberger J: Continuous assessment of cerebrovascular autoregulation after traumatic brain injury using brain tissue oxygen pressure reactivity. **Crit Care Med 34:**1783-1788, 2006

162. Jaeger M, Schuhmann MU, Soehle M, Nagel C, Meixensberger J: Continuous monitoring of cerebrovascular autoregulation after subarachnoid hemorrhage by brain tissue oxygen pressure reactivity and its relation to delayed cerebral infarction. **Stroke 38:**981-986, 2007

163. Jaeger M, Soehle M, Meixensberger J: Effects of decompressive craniectomy on brain tissue oxygen in patients with intracranial hypertension. **J Neurol Neurosurg Psychiatry 74:**513-515, 2003

164. Jaeger M, Soehle M, Schuhmann MU, Winkler D, Meixensberger J: Correlation of continuously monitored regional cerebral blood flow and brain tissue oxygen. **Acta Neurochir (Wien) 147:**51-6, 2005

165. Jennett B, Bond M: Assessment of outcome after severe brain damage. **Lancet 1**:480-484, 1975

166. Jensen RL, Hahn YS, Ciro E: Risk factors of intracranial pressure monitoring in children with fiberoptic devices: A critical review. **Surg Neurol 47:**16-22, 1997

167. Johnson DL, Krishnamurthy S: Severe pediatric head injury: Myth, magic, and actual fact. **Pediatr Neurosurg 28:**167-172, 1998

168. Johnston AJ, Steiner LA, Chatfield DA, Coles JP, Hutchinson PJ, Al-Rawi PG, et al: Effect of cerebral perfusion pressure augmentation with dopamine and norepinephrine on global and focal brain oxygenation after traumatic brain injury. **Intensive Care Med 30**:791-797, 2004

169. Johnston AJ, Steiner LA, Coles JP, Chatfield DA, Fryer TD, Smielewski P, et al: Effect of cerebral perfusion pressure augmentation on regional oxygenation and metabolism after head injury. **Crit Care Med 33**:189-95, 2005

170. Jones PA, Andrews PJ, Easton VJ, Minns RA: Traumatic brain injury in childhood: Intensive care time series data and outcome. **Br J Neurosurg 17**:29-39, 2003

171. Josan VA, Sgouros S: Early decompressive craniectomy may be effective in the treatment of refractory intracranial hypertension after traumatic brain injury. **Childs Nerv Syst 22:**1268-1274, 2006

172. Kan P, Amini A, Hansen K, White GL,Jr, Brockmeyer DL, Walker ML, et al: Outcomes after decompressive craniectomy for severe traumatic brain injury in children. **J Neurosurg 105:**337-342, 2006

173. Kelly DF, Martin NA, Kordestani R, Counelis G, Hovda DA, Bergsneider M, et al: Cerebral blood flow as a predictor of outcome following traumatic brain injury. **J Neurosurg 86:**633-641, 1997

174. Kett-White R, Hutchinson PJ, Al-Rawi PG, Czosnyka M, Gupta AK, Pickard JD, et al: Cerebral oxygen and microdialysis monitoring during aneurysm surgery: Effects of blood pressure, cerebrospinal fluid drainage, and temporary clipping on infarction. **J Neurosurg 96:**1013-1019, 2002

175. Kiening KL, Unterberg AW, Bardt TF, Schneider GH, Lanksch WR: Monitoring of cerebral oxygenation in patients with severe head injuries: Brain tissue PO2 versus jugular vein oxygen saturation. **J Neurosurg 85**:751-757, 1996

176. Kieslich M, Marquardt G, Galow G, Lorenz R, Jacobit G: Neurological and mental outcome after severe head injury in childhood: A long-term follow-up of 318 children. **Disabil Rehabil 23:**665-669, 2001

177. Klein HG, Spahn DR, Carson JL: Red blood cell transfusion in clinical practice. **Lancet 370:**415-426, 2007

178. Knudson MM, Lee S, Erickson V, Morabito D, Derugin N, Manley GT: Tissue oxygen monitoring during hemorrhagic shock and resuscitation: A comparison of lactated ringer's solution, hypertonic saline dextran, and HBOC-201. **J Trauma 54**:242-252, 2003

179. Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, et al: Duration of red-cell storage and complications after cardiac surgery. **N Engl J Med 358**:1229-1239, 2008

180. Kokoska ER, Smith GS, Pittman T, Weber TR: Early hypotension worsens neurological outcome in pediatric patients with moderately severe head trauma. **J Pediatr Surg 33:**333-338, 1998

181. Kontos HA, Wei EP, Navari RM, Levasseur JE, Rosenblum WI, Patterson JL,Jr: Responses of cerebral arteries and arterioles to acute hypotension and hypertension. **Am J Physiol 234:**H371-83, 1978

182. Kroppenstedt SN, Kern M, Thomale UW, Schneider GH, Lanksch WR, Unterberg AW: Effect of cerebral perfusion pressure on contusion volume following impact injury. **J Neurosurg 90:**520-526, 1999

183. Lacroix J, Hebert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T, et al: Transfusion strategies for patients in pediatric intensive care units. **N Engl J Med 356:**1609-1619, 2007

184. Lam JM, Hsiang JN, Poon WS: Monitoring of autoregulation using laser doppler flowmetry in patients with head injury. **J Neurosurg 86:**438-445, 1997

185. Lam WH, MacKersie A: Paediatric head injury: Incidence, aetiology and management. **Paediatr Anaesth 9:**377-385, 1999

186. Lang EW, Chesnut RM: A bedside method for investigating the integrity and critical thresholds of cerebral pressure autoregulation in severe traumatic brain injury patients. **Br J Neurosurg 14:**117-126, 2000

187. Lang EW, Czosnyka M, Mehdorn HM: Tissue oxygen reactivity and cerebral autoregulation after severe traumatic brain injury. **Crit Care Med 31:**267-271, 2003

188. Lang EW, Mulvey JM, Mudaliar Y, Dorsch NW: Direct cerebral oxygenation monitoring - a systematic review of recent publications. **Neurosurg Rev 30:**99-106, 2007

189. Langlois JA, Rutland-Brown W, Thomas KE: Traumatic brain injury in the United States: Emergency department visits, hospitalizations, and deaths. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, 2004

190. LASSEN NA: Cerebral blood flow and oxygen consumption in man. **Physiol Rev 39:**183-238, 1959

191. Latronico N, Beindorf AE, Rasulo FA, Febbrari P, Stefini R, Cornali C, et al: Limits of intermittent jugular bulb oxygen saturation monitoring in the management of severe head trauma patients. **Neurosurgery 46:**1131-8, 2000

192. Leal-Noval SR, Munoz-Gomez M, Arellano-Orden V, Marin-Caballos A, Amaya-Villar R, Marin A, et al: Impact of age of transfused blood on cerebral oxygenation in male patients with severe traumatic brain injury. **Crit Care Med 36:**1290-1296, 2008

193. Leal-Noval SR, Munoz-Gomez M, Murillo-Cabezas F: Optimal hemoglobin concentration in patients with subarachnoid hemorrhage, acute ischemic stroke and traumatic brain injury. **Curr Opin Crit Care 14:**156-162, 2008

194. Leal-Noval SR, Rincon-Ferrari MD, Marin-Niebla A, Cayuela A, Arellano-Orden V, Marin-Caballos A, et al: Transfusion of erythrocyte concentrates produces a variable increment on cerebral oxygenation in patients with severe traumatic brain injury: A preliminary study. **Intensive Care Med 32:**1733-1740, 2006

195. Lee JH, Kelly DF, Oertel M, McArthur DL, Glenn TC, Vespa P, et al: Carbon dioxide reactivity, pressure autoregulation, and metabolic suppression reactivity after head injury: A transcranial doppler study. **J Neurosurg 95:**222-232, 2001

196. Lee JH, Martin NA, Alsina G, McArthur DL, Zaucha K, Hovda DA, et al: Hemodynamically significant cerebral vasospasm and outcome after head injury: A prospective study. **J Neurosurg 87:**221-233, 1997

197. Leniger-Follert E, Lubbers DW, Wrabetz W: Regulation of local tissue PO2 of the brain cortex at different arterial O2 pressures. **Pflugers Arch 359:**81-95, 1975

198. Levin HS, Aldrich EF, Saydjari C, Eisenberg HM, Foulkes MA, Bellefleur M, et al: Severe head injury in children: Experience of the Traumatic Coma Data Bank. **Neurosurgery 31:**435-43, 1992

199. Levin HS, Wilde EA, Chu Z, Yallampalli R, Hanten GR, Li X, et al: Diffusion tensor imaging in relation to cognitive and functional outcome of traumatic brain injury in children. **J Head Trauma Rehabil 23:**197-208, 2008

200. Lewis S, Wong M, Myburgh J, Reilly P: Determining cerebral perfusion pressure thresholds in severe head trauma. **Acta Neurochir Suppl 71:**174-176, 1998

201. Lindegaard KF, Nornes H, Bakke SJ, Sorteberg W, Nakstad P: Cerebral vasospasm diagnosis by means of angiography and blood velocity measurements. **Acta Neurochir (Wien) 100:**12-24, 1989

202. Liu S, Liu W, Ding W, Miyake M, Rosenberg GA, Liu KJ: Electron paramagnetic resonance-guided normobaric hyperoxia treatment protects the brain by maintaining penumbral oxygenation in a rat model of transient focal cerebral ischemia. **J Cereb Blood Flow Metab 26:**1274-1284, 2006

203. Lobato RD, Rivas JJ, Gomez PA, Castaneda M, Canizal JM, Sarabia R, et al: Head-injured patients who talk and deteriorate into coma. analysis of 211 cases studied with computerized tomography. **J Neurosurg 75:**256-261, 1991

204. Longhi L, Valeriani V, Rossi S, De Marchi M, Egidi M, Stocchetti N: Effects of hyperoxia on brain tissue oxygen tension in cerebral focal lesions. **Acta Neurochir Suppl 81:**315-317, 2002

205. Luerssen TG, Garton HJ: Severe pediatric head injury: Myth, magic, and actual fact. concerning the article by Johnson and Krishnamurthy. **Pediatr Neurosurg 30:**55-56, 1999

206. Luerssen TG, Klauber MR, Marshall LF: Outcome from head injury related to patient's age. A longitudinal prospective study of adult and pediatric head injury. **J Neurosurg 68:**409-416, 1988

207. Maas AI, Fleckenstein W, de Jong DA, van Santbrink H: Monitoring cerebral oxygenation: Experimental studies and preliminary clinical results of continuous monitoring of cerebrospinal fluid and brain tissue oxygen tension. **Acta Neurochir Suppl (Wien) 59:**50-57, 1993

208. Maas AI, Stocchetti N, Bullock R: Moderate and severe traumatic brain injury in adults. **Lancet Neurol 7:**728-741, 2008

209. MacKenzie ET, McCulloch J, O'Kean M, Pickard JD, Harper AM: Cerebral circulation and norepinephrine: Relevance of the blood-brain barrier. **Am J Physiol 231:**483-488, 1976

210. Macmillan CS, Andrews PJ, Easton VJ: Increased jugular bulb saturation is associated with poor outcome in traumatic brain injury. **J Neurol Neurosurg Psychiatry 70:**101-104, 2001

211. Magnoni S, Ghisoni L, Locatelli M, Caimi M, Colombo A, Valeriani V, et al: Lack of improvement in cerebral metabolism after hyperoxia in severe head injury: A microdialysis study. **J Neurosurg 98:**952-958, 2003

212. Malone DL, Dunne J, Tracy JK, Putnam AT, Scalea TM, Napolitano LM: Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. **J Trauma 54:**898-905, 2003

213. Mandera M, Larysz D, Wojtacha M: Changes in cerebral hemodynamics assessed by transcranial doppler ultrasonography in children after head injury. **Childs Nerv Syst 18:**124-128, 2002

214. Manley GT, Hemphill JC, Morabito D, Derugin N, Erickson V, Pitts LH, et al: Cerebral oxygenation during hemorrhagic shock: Perils of hyperventilation and the therapeutic potential of hypoventilation. **J Trauma 48:**1025-32; discussion 1032-3, 2000

215. Manley GT, Hemphill JC, Morabito D, Erickson V, Holcroft JJ, Derugin N, et al: Small-volume resuscitation with the hemoglobin substitute HBOC-201: Effect on brain tissue oxygenation. **Adv Exp Med Biol 530:**311-317, 2003

216. Manley GT, Pitts LH, Morabito D, Doyle CA, Gibson J, Gimbel M, et al: Brain tissue oxygenation during hemorrhagic shock, resuscitation, and alterations in ventilation. **J Trauma 46:**261-267, 1999

217. Marik PE, Corwin HL: Efficacy of red blood cell transfusion in the critically ill: A systematic review of the literature. **Crit Care Med:** Aug 1, E-Pub ahead of print, 2008

218. Marik PE, Sibbald WJ: Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. **JAMA 269:**3024-3029, 1993

219. Marin-Caballos AJ, Murillo-Cabezas F, Cayuela-Dominguez A, Dominguez-Roldan JM, Rincon-Ferrari MD, Valencia-Anguita J, et al: Cerebral perfusion pressure and risk of brain hypoxia in severe head injury: A prospective observational study. **Crit Care 9**:R670-6, 2005

220. Marino R, Gasparotti R, Pinelli L, Manzoni D, Gritti P, Mardighian D, et al: Posttraumatic cerebral infarction in patients with moderate or severe head trauma. **Neurology 67**:1165-1171, 2006

221. Marmarou A, Fatouros PP, Barzo P, Portella G, Yoshihara M, Tsuji O, et al: Contribution of edema and cerebral blood volume to traumatic brain swelling in head-injured patients. **J Neurosurg 93**:183-193, 2000

222. Marmarou A, Signoretti S, Fatouros PP, Portella G, Aygok GA, Bullock MR: Predominance of cellular edema in traumatic brain swelling in patients with severe head injuries. **J Neurosurg 104**:720-730, 2006

223. Marshall LF, Bowers Marshall S, Klauber MR, et al.: A new classification of head injury based on computerized tomography. **J Neurosurg 75**:S14-S20, 1991

224. Marshall LF, Smith RW, Shapiro HM: The outcome with aggressive treatment in severe head injuries. Part I: The significance of intracranial pressure monitoring. **J Neurosurg 50**:20-25, 1979

225. Marshall RS: The functional relevance of cerebral hemodynamics: Why blood flow matters to the injured and recovering brain. **Curr Opin Neurol 17**:705-709, 2004

226. Martin JA, Kung HC, Mathews TJ, Hoyert DL, Strobino DM, Guyer B, et al: Annual summary of vital statistics: 2006. **Pediatrics 121**:788-801, 2008

227. Martin NA, Doberstein C, Zane C, Caron MJ, Thomas K, Becker DP: Posttraumatic cerebral arterial spasm: Transcranial doppler ultrasound, cerebral blood flow, and angiographic findings. **J Neurosurg 77**:575-583, 1992

228. Martin NA, Patwardhan RV, Alexander MJ, Africk CZ, Lee JH, Shalmon E, et al: Characterization of cerebral hemodynamic phases following severe head trauma: Hypoperfusion, hyperemia, and vasospasm. **J Neurosurg 87**:9-19, 1997

229. Marton E, Mazzucco M, Nascimben E, Martinuzzi A, Longatti P: Severe head injury in early infancy: Analysis of causes and possible predictive factors for outcome. **Childs Nerv Syst 23:**873-880, 2007

230. Mayer T, Walker ML, Johnson DG, Matlak ME: Causes of morbidity and mortality in severe pediatric trauma. **JAMA 245:**719-721, 1981

231. McCarthy ML, MacKenzie EJ, Durbin DR, Aitken ME, Jaffe KM, Paidas CN, et al: The Pediatric Quality of Life inventory: An evaluation of its reliability and validity for children with traumatic brain injury. **Arch Phys Med Rehabil 86:**1901-1909, 2005

232. McIntyre LA, Fergusson DA, Hutchison JS, Pagliarello G, Marshall JC, Yetisir E, et al: Effect of a liberal versus restrictive transfusion strategy on mortality in patients with moderate to severe head injury. **Neurocrit Care 5:**4-9, 2006

233. Meixensberger J, Dings J, Kuhnigk H, Roosen K: Studies of tissue PO2 in normal and pathological human brain cortex. **Acta Neurochir Suppl (Wien) 59:**58-63, 1993

234. Meixensberger J, Jaeger M, Vath A, Dings J, Kunze E, Roosen K: Brain tissue oxygen guided treatment supplementing ICP/CPP therapy after traumatic brain injury. **J Neurol Neurosurg Psychiatry 74:**760-764, 2003

235. Menon DK, Coles JP, Gupta AK, Fryer TD, Smielewski P, Chatfield DA, et al: Diffusion limited oxygen delivery following head injury. **Crit Care Med 32:**1384-1390, 2004

236. Menzel M, Doppenberg EM, Zauner A, Soukup J, Reinert MM, Clausen T, et al: Cerebral oxygenation in patients after severe head injury: Monitoring and effects of arterial hyperoxia on cerebral blood flow, metabolism and intracranial pressure. **J Neurosurg Anesthesiol 11:**240-251, 1999

237. Menzel M, Soukup J, Henze D, Clausen T, Marx T, Hillman A, et al: Brain tissue oxygen monitoring for assessment of autoregulation: Preliminary results suggest a new hypothesis. **J Neurosurg Anesthesiol 15:**33-41, 2003

238. Meyer PG, Ducrocq S, Rackelbom T, Orliaguet G, Renier D, Carli P: Surgical evacuation of acute subdural hematoma improves cerebral hemodynamics in children: A transcranial doppler evaluation. **Childs Nerv Syst 21:**133-137, 2005

239. Mirvis SE, Wolf AL, Numaguchi Y, Corradino G, Joslyn JN: Posttraumatic cerebral infarction diagnosed by CT: Prevalence, origin, and outcome. **AJR Am J Roentgenol 154:**1293-1298, 1990

240. Monteiro LM, Bollen CW, van Huffelen AC, Ackerstaff RG, Jansen NJ, van Vught AJ: Transcranial doppler ultrasonography to confirm brain death: A meta-analysis. **Intensive Care Med 32:**1937-1944, 2006

241. Morais DF, Spotti AR, Tognola WA, Gaia FF, Andrade AF: Clinical application of magnetic resonance in acute traumatic brain injury. **Arq Neuropsiquiatr 66:**53-58, 2008

242. Moreno JA, Mesalles E, Gener J, Tomasa A, Ley A, Roca J, et al: Evaluating the outcome of severe head injury with transcranial doppler ultrasonography. **Neurosurg Focus 8:**e8, 2000

243. Morris KP, Forsyth RJ, Parslow RC, Tasker RC, Hawley CA, UK Paediatric Traumatic Brain Injury Study Group, et al: Intracranial pressure complicating severe traumatic brain injury in children: Monitoring and management. **Intensive Care Med 32:**1606-1612, 2006

244. Morrison WE, Arbelaez JJ, Fackler JC, De Maio A, Paidas CN: Gender and age effects on outcome after pediatric traumatic brain injury. **Pediatr Crit Care Med 5:**145-151, 2004

245. Muizelaar JP, Marmarou A, DeSalles AA, Ward JD, Zimmerman RS, Li Z, et al: Cerebral blood flow and metabolism in severely head-injured children. Part 1: Relationship with GCS score, outcome, ICP, and PVI. **J Neurosurg 71:**63-71, 1989

246. Muizelaar JP, Marmarou A, Ward JD, Kontos HA, Choi SC, Becker DP, et al: Adverse effects of prolonged hyperventilation in patients with severe head injury: A randomized clinical trial. **J Neurosurg 75:**731-739, 1991

247. Muizelaar JP, Ward JD, Marmarou A, Newlon PG, Wachi A: Cerebral blood flow and metabolism in severely head-injured children. Part 2: Autoregulation. **J Neurosurg 71:**72-76, 1989

248. Myburgh JA, Upton RN, Grant C, Martinez A: A comparison of the effects of norepinephrine, epinephrine, and dopamine on cerebral blood flow and oxygen utilisation. **Acta Neurochir Suppl 71:**19-21, 1998

249. Nadvi SS, Du Trevou MD, Van Dellen JR, Gouws E: The use of transcranial doppler ultrasonography as a method of assessing intracranial pressure in hydrocephalic children. **Br J Neurosurg 8:**573-577, 1994

250. Nagdyman N, Fleck T, Barth S, Abdul-Khaliq H, Stiller B, Ewert P, et al: Relation of cerebral tissue oxygenation index to central venous oxygen saturation in children. **Intensive Care Med 30:**468-471, 2004

251. Nagdyman N, Fleck T, Schubert S, Ewert P, Peters B, Lange PE, et al: Comparison between cerebral tissue oxygenation index measured by near-infrared spectroscopy and venous jugular bulb saturation in children. **Intensive Care Med 31:**846-850, 2005

252. Narayan RK, Kishore PR, Becker DP, Ward JD, Enas GG, Greenberg RP, et al: Intracranial pressure: To monitor or not to monitor? A review of our experience with severe head injury. **J Neurosurg 56:**650-659, 1982

253. Narotam PK, Burjonrappa SC, Raynor SC, Rao M, Taylon C: Cerebral oxygenation in major pediatric trauma: Its relevance to trauma severity and outcome. **J Pediatr Surg 41:**505-513, 2006

254. Newell DW, Aaslid R, Lam A, Mayberg TS, Winn HR: Comparison of flow and velocity during dynamic autoregulation testing in humans. **Stroke 25:**793-797, 1994

255. Newell DW, Aaslid R, Stooss R, Seiler RW, Reulen HJ: Evaluation of hemodynamic responses in head injury patients with transcranial doppler monitoring. **Acta Neurochir (Wien) 139:**804-817, 1997

256. Ng SC, Poon WS, Chan MT, Lam JM, Lam W, Metreweli C: Transcranial doppler ultrasonography (TCD) in ventilated head injured patients: Correlation with stable xenon-enhanced CT. **Acta Neurochir Suppl 76:**479-482, 2000

257. Ng SC, Poon WS, Chan MT, Lam JM, Lam WW: Is transcranial doppler ultrasonography (TCD) good enough in determining CO2 reactivity and pressure autoregulation in head-injured patients? **Acta Neurochir Suppl 81:**125-127, 2002

258. Niedzwecki CM, Marwitz JH, Ketchum JM, Cifu DX, Dillard CM, Monasterio EA: Traumatic brain injury: A comparison of inpatient functional outcomes between children and adults. **J Head Trauma Rehabil 23:**209-219, 2008

259. Nishimura N, Iwasaki K, Ogawa Y, Shibata S: Oxygen administration, cerebral blood flow velocity, and dynamic cerebral autoregulation. **Aviat Space Environ Med 78:**1121-1127, 2007

260. Nordstrom CH: Assessment of critical thresholds for cerebral perfusion pressure by performing bedside monitoring of cerebral energy metabolism. **Neurosurg Focus 15:**E5, 2003

261. Nordstrom CH: Assessment of the optimal cerebral perfusion pressure in head-injured patients. **Anesth Analg 101:**299-300, 2005

262. Nordstrom CH: Cerebral perfusion pressure between 50 and 60 mmHg may be beneficial in head-injured patients: A computerized secondary insult monitoring study. **Neurosurgery 58:**E590; author reply E590, 2006

263. Nortje J, Coles JP, Timofeev I, Fryer TD, Aigbirhio FI, Smielewski P, et al: Effect of hyperoxia on regional oxygenation and metabolism after severe traumatic brain injury: Preliminary findings. **Crit Care Med 36:** 273-281, 2007

264. Oertel M, Boscardin WJ, Obrist WD, Glenn TC, McArthur DL, Gravori T, et al: Posttraumatic vasospasm: The epidemiology, severity, and time course of an underestimated phenomenon: A prospective study performed in 299 patients. **J Neurosurg 103:**812-824, 2005

265. Oertel M, Kelly DF, Lee JH, McArthur DL, Glenn TC, Vespa P, et al: Efficacy of hyperventilation, blood pressure elevation, and metabolic suppression therapy in controlling intracranial pressure after head injury. **J Neurosurg 97:**1045-1053, 2002

266. Oluigbo CO, Gan YC, Sgouros S, Chapman S, Kay A, Solanki G, et al: Pattern, management and outcome of cervical spine injuries associated with head injuries in paediatric patients. **Childs Nerv Syst 24:**87-92, 2008

267. Palmer S, Bader MK: Brain tissue oxygenation in brain death. **Neurocrit Care 2:**17-22, 2005

268. Panerai RB: Assessment of cerebral pressure autoregulation in humans - a review of measurement methods. **Physiol Meas 19:**305-338, 1998

269. Panerai RB, Kerins V, Fan L, Yeoman PM, Hope T, Evans DH: Association between dynamic cerebral autoregulation and mortality in severe head injury. **Br J Neurosurg 18:**471-479, 2004

270. Pang D: Spinal cord injury without radiographic abnormality in children, 2 decades later. **Neurosurgery 55:**1325-42, 2004

271. Patel HC, Menon DK, Tebbs S, Hawker R, Hutchinson PJ, Kirkpatrick PJ: Specialist neurocritical care and outcome from head injury. **Intensive Care Med 28:**547-553, 2002

272. Paulson OB, Strandgaard S, Edvinsson L: Cerebral autoregulation. **Cerebrovasc Brain Metab Rev 2:**161-192, 1990

273. Pigula FA, Wald SL, Shackford SR, Vane DW: The effect of hypotension and hypoxia on children with severe head injuries. **J Pediatr Surg 28:**310-4, 1993

274. Pillai S, Praharaj SS, Mohanty A, Kolluri VR: Prognostic factors in children with severe diffuse brain injuries: A study of 74 patients. **Pediatr Neurosurg 34:**98-103, 2001

275. Plotz FB, Kneyber M, van Heerde M, Markhorst D: Traumatic pediatric brain injury and intracranial pressure monitoring: Does it really improve outcome? **Intensive Care Med 33:**1675, 2007

276. Pollack MM, Patel KM, Ruttimann UE: PRISM III: An updated pediatric risk of mortality score. **Crit Care Med 24:**743-752, 1996

277. Pople IK, Quinn MW, Bayston R, Hayward RD: The doppler pulsatility index as a screening test for blocked ventriculo-peritoneal shunts. **Eur J Pediatr Surg 1 Suppl 1:**27-29, 1991

278. Prabhakaran P, Reddy AT, Oakes WJ, King WD, Winkler MK, Givens TG: A pilot trial comparing cerebral perfusion pressure-targeted therapy to intracranial pressure-targeted therapy in children with severe traumatic brain injury. **J Neurosurg 100:**454-459, 2004

279. Prabhu SS, Zauner A, Bullock MR: Surgical management of traumatic brain injury. *In* Winn HR (ed) **Youman's Neurological Surgery,** Philadelphia: Elsevier Inc., 2004, pp 5145-5180

280. Prasad MR, Ewing-Cobbs L, Swank PR, Kramer L: Predictors of outcome following traumatic brain injury in young children. **Pediatr Neurosurg 36:**64-74, 2002

281. Puppo C, Lopez L, Caragna E, Biestro A: One-minute dynamic cerebral autoregulation in severe head injury patients and its comparison with static autoregulation. A transcranial doppler study. **Neurocrit Care 8:**344-352, 2008

282. Raat NJ, Ince C: Oxygenating the microcirculation: The perspective from blood transfusion and blood storage. **Vox Sang 93:**12-18, 2007

283. Ract C, Le Moigno S, Bruder N, Vigue B: Transcranial doppler ultrasound goal-directed therapy for the early management of severe traumatic brain injury. **Intensive Care Med 33:**645-651, 2007

284. Ract C, Vigue B: Comparison of the cerebral effects of dopamine and norepinephrine in severely head-injured patients. **Intensive Care Med 27:**101-106, 2001

285. Ract C, Vigue B, Bodjarian N, Mazoit JX, Samii K, Tadie M: Comparison of dopamine and norepinephrine after traumatic brain injury and hypoxic-hypotensive insult. **J Neurotrauma 18:**1247-1254, 2001

286. Raimondi AJ, Di Rocco C: Cerebral angiography in meningocerbral inflammatory diseases in infancy and childhood: A study of thirty-five cases. **Neurosurgery 3:**37-44, 1978

287. Ransom GH, Mann FA, Vavilala MS, Haruff R, Rivara FP: Cerebral infarct in head injury: Relationship to child abuse. **Child Abuse Negl 27:**381-392, 2003

288. Reiles E, Van der Linden P: Transfusion trigger in critically ill patients: Has the puzzle been completed? **Crit Care 11:**142, 2007

289. Reinert M, Barth A, Rothen HU, Schaller B, Takala J, Seiler RW: Effects of cerebral perfusion pressure and increased fraction of inspired oxygen on brain tissue oxygen, lactate and glucose in patients with severe head injury. **Acta Neurochir (Wien) 145:**341-9, 2003

290. Reinert M, Schaller B, Widmer HR, Seiler R, Bullock R: Influence of oxygen therapy on glucose-lactate metabolism after diffuse brain injury. **J Neurosurg 101:**323-329, 2004

291. Reithmeier T, Lohr M, Pakos P, Ketter G, Ernestus RI: Relevance of ICP and ptiO2 for indication and timing of decompressive craniectomy in patients with malignant brain edema. **Acta Neurochir (Wien) 147:**947-51, 2005

292. Richards DA, Tolias CM, Sgouros S, Bowery NG: Extracellular glutamine to glutamate ratio may predict outcome in the injured brain: A clinical microdialysis study in children. **Pharmacol Res 48:**101-109, 2003

293. Robertson C: Critical care management of traumatic brain injury, *In* Winn HR (ed): **Youmans Neurological Surgery,** Philadelphia: Elsevier Inc., pp 5103-5144

294. Robertson CS, Valadka AB, Hannay HJ, Contant CF, Gopinath SP, Cormio M, et al: Prevention of secondary ischemic insults after severe head injury. **Crit Care Med 27:**2086-2095, 1999

295. Robinson WP,3rd, Ahn J, Stiffler A, Rutherford EJ, Hurd H, Zarzaur BL, et al: Blood transfusion is an independent predictor of increased mortality in nonoperatively managed blunt hepatic and splenic injuries. **J Trauma 58:**437-44, 2005

296. Rosenthal G, Hemphill JC,3rd, Sorani M, Martin C, Morabito D, Obrist WD, et al: Brain tissue oxygen tension is more indicative of oxygen diffusion than oxygen delivery and metabolism in patients with traumatic brain injury. **Crit Care Med 36:**1917-1924,2008

297. Rosenthal G, Hemphill JC, Sorani M, Martin C, Morabito D, Meeker M, et al: The role of lung function in brain tissue oxygenation following traumatic brain injury. **J Neurosurg 108:**59-65, 2008

298. Rosenthal G, Morabito D, Cohen M, Roeytenberg A, Derugin N, Panter SS, et al: Use of hemoglobin-based oxygen-carrying solution-201 to improve resuscitation parameters and prevent

secondary brain injury in a swine model of traumatic brain injury and hemorrhage: Laboratory investigation. **J Neurosurg 108:**575-587, 2008

299. Rosner B, Prineas RJ, Loggie JM, Daniels SR: Blood pressure nomograms for children and adolescents, by height, sex, and age, in the united states. **J Pediatr 123:**871-886, 1993

300. Rosner MJ, Daughton S: Cerebral perfusion pressure management in head injury. **J Trauma 30:**933-40, 1990

301. Rosner MJ, Rosner SD, Johnson AH: Cerebral perfusion pressure: Management protocol and clinical results. **J Neurosurg 83:**949-962, 1995

302. Rossi S, Balestreri M, Spagnoli D, Bellinzona G, Valeriani V, Bruzzone P, et al: Oxygen delivery and oxygen tension in cerebral tissue during global cerebral ischaemia: A swine model. **Acta Neurochir Suppl 76:**199-202, 2000

303. Rossi S, Stocchetti N, Longhi L, Balestreri M, Spagnoli D, Zanier ER, et al: Brain oxygen tension, oxygen supply, and oxygen consumption during arterial hyperoxia in a model of progressive cerebral ischemia. **J Neurotrauma 18:**163-174, 2001

304. Ruf B, Heckmann M, Schroth I, Hugens-Penzel M, Reiss I, Borkhardt A, et al: Early decompressive craniectomy and duraplasty for refractory intracranial hypertension in children: Results of a pilot study. **Crit Care 7:**R133-8, 2003

305. Saatman KE, Duhaime AC, Bullock R, Maas AI, Valadka A, Manley GT, et al: Classification of traumatic brain injury for targeted therapies. **J Neurotrauma 25:**719-738, 2008

306. Sahuquillo J, Munar F, Baguena M, Poca MA, Pedraza S, Rodriguez-Baeza A: Evaluation of cerebrovascular CO2-reactivity and autoregulation in patients with post-traumatic diffuse brain swelling (diffuse injury III). **Acta Neurochir Suppl 71:**233-236, 1998

307. Sakas DE, Bullock MR, Patterson J, Hadley D, Wyper DJ, Teasdale GM: Focal cerebral hyperemia after focal head injury in humans: A benign phenomenon? **J Neurosurg 83:**277-284, 1995

308. Salorio CF, Slomine BS, Guerguerian AM, Christensen JR, White JR, Natale JE, et al: Intensive care unit variables and outcome after pediatric traumatic brain injury: A retrospective study of survivors. **Pediatr Crit Care Med 9**:47-53, 2008

309. Samant UB, Mack CD, Koepsell T, Rivara FP, Vavilala MS: Time of hypotension and discharge outcome in children with severe traumatic brain injury. **J Neurotrauma 25**:495-502, 2008

310. Sanker P, Richard KE, Weigl HC, Klug N, van Leyen K: Transcranial doppler sonography and intracranial pressure monitoring in children and juveniles with acute brain injuries or hydrocephalus. **Childs Nerv Syst 7**:391-393, 1991

311. Sarrafzadeh AS, Kiening KL, Bardt TF, Schneider GH, Unterberg AW, Lanksch WR: Cerebral oxygenation in contusioned vs. nonlesioned brain tissue: Monitoring of PtiO2 with Licox and Paratrend. **Acta Neurochir Suppl 71**:186-189, 1998

312. Scheufler KM, Lehnert A, Rohrborn HJ, Nadstawek J, Thees C: Individual value of brain tissue oxygen pressure, microvascular oxygen saturation, cytochrome redox level, and energy metabolites in detecting critically reduced cerebral energy state during acute changes in global cerebral perfusion. **J Neurosurg Anesthesiol 16**:210-219, 2004

313. Scheufler KM, Rohrborn HJ, Zentner J: Does tissue oxygen-tension reliably reflect cerebral oxygen delivery and consumption? **Anesth Analg 95**:1042-8, 2002

314. Schmidt EA, Czosnyka M, Gooskens I, Piechnik SK, Matta BF, Whitfield PC, et al: Preliminary experience of the estimation of cerebral perfusion pressure using transcranial doppler ultrasonography. **J Neurol Neurosurg Psychiatry 70**:198-204, 2001

315. Schmidt EA, Czosnyka M, Steiner LA, Balestreri M, Smielewski P, Piechnik SK, et al: Asymmetry of pressure autoregulation after traumatic brain injury. **J Neurosurg 99**:991-998, 2003

316. Schneider GH, Sarrafzadeh AS, Kiening KL, Bardt TF, Unterberg AW, Lanksch WR: Influence of hyperventilation on brain tissue-PO2, PCO2, and pH in patients with intracranial hypertension. **Acta Neurochir Suppl 71**:62-65, 1998

317. Schoeman JF, Laubscher JA, Donald PR: Serial lumbar CSF presure measurements and cranial computed tomographic findings in childhood tuberculous meningitits. **Childs Nerv Syst 16:**203-8, 2000

318. Schoeman JF, Van Zyl LE, Laubscher JA, Donald PR: Serial CT scanning in childhood tuberculous meningitis: Prognostic features in 198 cases. **J Child Neurol 10:**320-329, 1995

319. Schwarz G, Litscher G, Kleinert R, Jobstmann R: Cerebral oximetry in dead subjects. **J Neurosurg Anesthesiol 8:**189-193, 1996

320. Segui-Gomez M, MacKenzie EJ: Measuring the public health impact of injuries. **Epidemiol Rev 25:**3-19, 2003

321. Semple PL, Bass DH, Peter JC: Severe head injury in children - a preventable but forgotten epidemic. **S Afr Med J 88:**440-444, 1998

322. Shafi S, de la Plata CM, Diaz-Arrastia R, Bransky A, Frankel H, Elliott AC, et al: Ethnic disparities exist in trauma care. **J Trauma 63:**1138-1142, 2007

323. Shafi S, Diaz-Arrastia R, Madden C, Gentilello L: Intracranial pressure monitoring in brain-injured patients is associated with worsening of survival. **J Trauma 64:**335-340, 2008

324. Shah CV, Localio AR, Lanken PN, Kahn JM, Bellamy S, Gallop R, et al: The impact of development of acute lung injury on hospital mortality in critically ill trauma patients. **Crit Care Med 36:**2309-2315, 2008

325. Shapiro K, Marmarou A: Clinical applications of the pressure-volume index in treatment of pediatric head injuries. **J Neurosurg 56:**819-825, 1982

326. Shapiro S, Bowman R, Callahan J, Wolfla C: The fiberoptic intraparenchymal cerebral pressure monitor in 244 patients. **Surg Neurol 45:**278-282, 1996

327. Sharples PM, Matthews DS, Eyre JA: Cerebral blood flow and metabolism in children with severe head injuries. part 2: Cerebrovascular resistance and its determinants. **J Neurol Neurosurg Psychiatry 58:**153-159, 1995

328. Sharples PM, Storey A, Aynsley-Green A, Eyre JA: Avoidable factors contributing to death of children with head injury. **BMJ 300:**87-91, 1990

329. Sharples PM, Stuart AG, Matthews DS, Aynsley-Green A, Eyre JA: Cerebral blood flow and metabolism in children with severe head injury. Part 1: Relation to age, glasgow coma score, outcome, intracranial pressure, and time after injury. **J Neurol Neurosurg Psychiatry 58:**145-152, 1995

330. Shin HK, Dunn AK, Jones PB, Boas DA, Lo EH, Moskowitz MA, et al: Normobaric hyperoxia improves cerebral blood flow and oxygenation, and inhibits peri-infarct depolarizations in experimental focal ischaemia. **Brain 130:**1631-1642, 2007

331. Shin HK, Nishimura M, Jones PB, Ay H, Boas DA, Moskowitz MA, et al: Mild induced hypertension improves blood flow and oxygen metabolism in transient focal cerebral ischemia. **Stroke39:**1548-1555, 2008

332. Siegemund M, van Bommel J, Ince C: Assessment of regional tissue oxygenation. **Intensive Care Med 25:**1044-1060, 1999

333. Siesjo BK: Pathophysiology and treatment of focal cerebral ischemia. Part I: Pathophysiology. **J Neurosurg 77:**169-184, 1992

334. Signorini DF, Andrews PJ, Jones PA, Wardlaw JM, Miller JD: Adding insult to injury: The prognostic value of early secondary insults for survival after traumatic brain injury. **J Neurol Neurosurg Psychiatry 66:**26-31, 1999

335. Simpson D, Reilly P: Pediatric coma scale. **Lancet 2:**450, 1982

336. Simpson DA, Cockington RA, Hanieh A, Raftos J, Reilly PL: Head injuries in infants and young children: The value of the Paediatric Coma Scale. Review of literature and report on a study. **Childs Nerv Syst 7:**183-190, 1991

337. Slater A, Shann F, Pearson G, Paediatric Index of Mortality (PIM) Study Group: PIM2: A revised version of the paediatric index of mortality. **Intensive Care Med 29:**278-285, 2003

338. Smith MJ, Stiefel MF, Magge S, Frangos S, Bloom S, Gracias V, et al: Packed red blood cell transfusion increases local cerebral oxygenation. **Crit Care Med 33:**1104-1108, 2005

339. Smith ML, Counelis GJ, Maloney-Wilensky E, Stiefel MF, Donley K, Leroux PD: Brain tissue oxygen tension in clinical brain death: A case series. **Neurol Res 29:**755-7599, 2007

340. Snyder RD, Stovring J, Cushing AH, Davis LE, Hardy TL: Cerebral infarction in childhood bacterial meningitis. **J Neurol Neurosurg Psychiatry 44:**581-585, 1981

341. Sokrab TE, Johansson BB: Regional cerebral blood flow in acute hypertension induced by adrenaline, noradrenaline and phenylephrine in the conscious rat. **Acta Physiol Scand 137:**101-106, 1989

342. Sola A, Rogido MR, Deulofeut R: Oxygen as a neonatal health hazard: Call for detente in clinical practice. **Acta Paediatr 96:**801-812, 2007

343. Soustiel JF, Sviri GE: Monitoring of cerebral metabolism: Non-ischemic impairment of oxidative metabolism following severe traumatic brain injury. **Neurol Res 29:**654-660, 2007

344. Splavski B, Radanovic B, Vrankovic D, Has B, Muzevic D, Janculjak D, et al: Transcranial doppler ultrasonography as an early outcome forecaster following severe brain injury. **Br J Neurosurg 20:**386-390, 2006

345. Steiner LA, Coles JP, Czosnyka M, Minhas PS, Fryer TD, Aigbirhio FI, et al: Cerebrovascular pressure reactivity is related to global cerebral oxygen metabolism after head injury. **J Neurol Neurosurg Psychiatry 74:**765-770, 2003

346. Steiner LA, Coles JP, Johnston AJ, Chatfield DA, Smielewski P, Fryer TD, et al: Assessment of cerebrovascular autoregulation in head-injured patients: A validation study. **Stroke 34:**2404-2409, 2003

347. Steiner LA, Czosnyka M, Piechnik SK, Smielewski P, Chatfield D, Menon DK, et al: Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. **Crit Care Med 30:**733-738, 2002

348. Steiner LA, Johnston AJ, Czosnyka M, Chatfield DA, Salvador R, Coles JP, et al: Direct comparison of cerebrovascular effects of norepinephrine and dopamine in head-injured patients. **Crit Care Med 32:**1049-1054, 2004

349. Stiefel MF, Heuer GG, Smith MJ, Bloom S, Maloney-Wilensky E, Gracias VH, et al: Cerebral oxygenation following decompressive hemicraniectomy for the treatment of refractory intracranial hypertension. **J Neurosurg 101:**241-247, 2004

350. Stiefel MF, Spiotta A, Gracias VH, Garuffe AM, Guillamondegui O, Maloney-Wilensky E, et al: Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. **J Neurosurg 103:**805-811, 2005

351. Stiefel MF, Udoetuk JD, Spiotta AM, Gracias VH, Goldberg A, Maloney-Wilensky E, et al: Conventional neurocritical care and cerebral oxygenation after traumatic brain injury. **J Neurosurg 105:**568-575, 2006

352. Stiefel MF, Udoetuk JD, Storm PB, Sutton LN, Kim H, Dominguez TE, et al: Brain tissue oxygen monitoring in pediatric patients with severe traumatic brain injury. **J Neurosurg 105:**281-286, 2006

353. Stocchetti N, Chieregato A, De Marchi M, Croci M, Benti R, Grimoldi N: High cerebral perfusion pressure improves low values of local brain tissue O2 tension (PtiO2) in focal lesions. **Acta Neurochir Suppl 71:**162-165, 1998

354. Stocchetti N, Pagan F, Calappi E, Canavesi K, Beretta L, Citerio G, et al: Inaccurate early assessment of neurological severity in head injury. **J Neurotrauma 21:**1131-1140, 2004

355. Stocchetti N, Rossi S: Re: Limits of intermittent jugular bulb oxygen saturation monitoring in the management of severe head trauma patients. **Neurosurgery 48:**454-456, 2001

356. Strebel S, Lam AM, Matta B, Mayberg TS, Aaslid R, Newell DW: Dynamic and static cerebral autoregulation during isoflurane, desflurane, and propofol anesthesia. **Anesthesiology 83:**66-76, 1995

357. Stylianos S, Ford HR: Outcomes in pediatric trauma care. **Semin Pediatr Surg 17:**110-115, 2008

358. Suttner S, Piper SN, Kumle B, Lang K, Rohm KD, Isgro F, et al: The influence of allogeneic red blood cell transfusion compared with 100% oxygen ventilation on systemic oxygen transport and skeletal muscle oxygen tension after cardiac surgery. **Anesth Analg 99:**2-11, 2004

359. Tawil I, Stein DM, Mirvis SE, Scalea TM: Posttraumatic cerebral infarction: Incidence, outcome, and risk factors. **J Trauma 64:**849-853, 2008

360. Taylor A, Butt W, Rosenfeld J, Shann F, Ditchfield M, Lewis E, et al: A randomized trial of very early decompressive craniectomy in children with traumatic brain injury and sustained intracranial hypertension. **Childs Nerv Syst 17:**154-162, 2001

361. Taylor RW, O'Brien J, Trottier SJ, Manganaro L, Cytron M, Lesko MF, et al: Red blood cell transfusions and nosocomial infections in critically ill patients. **Crit Care Med 34:**2302-8, 2006

362. Teasdale G, Jennett B: Assessment and prognosis of coma after head injury. **Acta Neurochir (Wien) 34:**45-55, 1976

363. Tepas JJ,3rd, DiScala C, Ramenofsky ML, Barlow B: Mortality and head injury: The pediatric perspective. **J Pediatr Surg 25:**92-5, 1990

364. Tepas JJ,3rd, Mollitt DL, Talbert JL, Bryant M: The pediatric trauma score as a predictor of injury severity in the injured child. **J Pediatr Surg 22:**14-18, 1987

365. Tepas JJ,3rd, Ramenofsky ML, Mollitt DL, Gans BM, DiScala C: The pediatric trauma score as a predictor of injury severity: An objective assessment. **J Trauma 28:**425-429, 1988

366. ter Minassian A, Melon E, Leguerinel C, Lodi CA, Bonnet F, Beydon L: Changes in cerebral blood flow during PaCO2 variations in patients with severe closed head injury: Comparison between the Fick and transcranial doppler methods. **J Neurosurg 88:**996-1001, 1998

367. Teruel GC, Rico AP, Cambra Lasaosa FJ, Temprano AC, Julian AN, Costa Clara JM: Severe head injury among children: Computed tomography evaluation as a prognostic factor. **J Pediatr Surg 42:**1903-1906, 2007

368. Thees C, Scheufler KM, Nadstawek J, Zentner J, Lehnert A, Hoeft A: Monitoring of cerebral perfusion pressure during intracranial hypertension: A sufficient parameter of adequate cerebral perfusion and oxygenation? **Intensive Care Med 29:**386-390, 2003

369. Tiecks FP, Lam AM, Aaslid R, Newell DW: Comparison of static and dynamic cerebral autoregulation measurements. **Stroke 26:**1014-1019, 1995

370. Tilford JM, Aitken ME, Anand KJ, Green JW, Goodman AC, Parker JG, et al: Hospitalizations for critically ill children with traumatic brain injuries: A longitudinal analysis. **Crit Care Med 33:**2074-2081, 2005

371. Tilford JM, Aitken ME, Goodman AC, Adelson PD: Measuring the cost-effectiveness of technologic change in the treatment of pediatric traumatic brain injury. **J Trauma 63:**S113-20, 2007

372. Tolias C, Richards D, Bowery N, Sgouros S: Investigation of extracellular amino acid release in children with severe head injury using microdialysis. A pilot study. **Acta Neurochir Suppl 81:**377-379, 2002

373. Tolias CM, Reinert M, Seiler R, Gilman C, Scharf A, Bullock MR: Normobaric hyperoxia--induced improvement in cerebral metabolism and reduction in intracranial pressure in patients with severe head injury: A prospective historical cohort-matched study. **J Neurosurg 101:**435-444, 2004

374. Tolias CM, Richards DA, Bowery NG, Sgouros S: Extracellular glutamate in the brains of children with severe head injuries: A pilot microdialysis study. **Childs Nerv Syst 18:**368-374, 2002

375. Tonnesen J, Pryds A, Larsen EH, Paulson OB, Hauerberg J, Knudsen GM: Laser doppler flowmetry is valid for measurement of cerebral blood flow autoregulation lower limit in rats. **Exp Physiol 90:**349-355, 2005

376. Tontisirin N, Armstead W, Waitayawinyu P, Moore A, Udomphorn Y, Zimmerman JJ, et al: Change in cerebral autoregulation as a function of time in children after severe traumatic brain injury: A case series. **Childs Nerv Syst 23:**1163-1169, 2007

377. Tornetta P,3rd, Mostafavi H, Riina J, Turen C, Reimer B, Levine R, et al: Morbidity and mortality in elderly trauma patients. **J Trauma 46:**702-706, 1999

378. Trabold F, Meyer PG, Blanot S, Carli PA, Orliaguet GA: The prognostic value of transcranial doppler studies in children with moderate and severe head injury. **Intensive Care Med 30:**108-112, 2004

379. Tuor UI, Edvinsson L, McCulloch J: Catecholamines and the relationship between cerebral blood flow and glucose use. **Am J Physiol 251:**H824-33, 1986

380. Udomphorn Y, Armstead WM, Vavilala MS: Cerebral blood flow and autoregulation after pediatric traumatic brain injury. **Pediatr Neurol 38:**225-234, 2008

381. Unterberg AW, Kiening KL, Hartl R, Bardt T, Sarrafzadeh AS, Lanksch WR: Multimodal monitoring in patients with head injury: Evaluation of the effects of treatment on cerebral oxygenation. **J Trauma 42:**S32-7, 1997

382. Ursino M, Di Giammarco P: A mathematical model of the relationship between cerebral blood volume and intracranial pressure changes: The generation of plateau waves. **Ann Biomed Eng 19:**15-42, 1991

383. Vajkoczy P, Roth H, Horn P, Lucke T, Thome C, Hubner U, et al: Continuous monitoring of regional cerebral blood flow: Experimental and clinical validation of a novel thermal diffusion microprobe. **J Neurosurg 93:**265-274, 2000

384. Valadka AB, Gopinath SP, Contant CF, Uzura M, Robertson CS: Relationship of brain tissue PO2 to outcome after severe head injury. **Crit Care Med 26:**1576-1581, 1998

385. Valadka AB, Hlatky R, Furuya Y, Robertson CS: Brain tissue PO2: Correlation with cerebral blood flow. **Acta Neurochir Suppl 81:**299-301, 2002

386. Vamvakas EC, Carven JH: Length of storage of transfused red cells and postoperative morbidity in patients undergoing coronary artery bypass graft surgery. **Transfusion 40:**101-109, 2000

387. van de Watering L, Lorinser J, Versteegh M, Westendord R, Brand A: Effects of storage time of red blood cell transfusions on the prognosis of coronary artery bypass graft patients. **Transfusion 46:**1712-1718, 2006

388. van den Brink WA, van Santbrink H, Steyerberg EW, Avezaat CJ, Suazo JA, Hogesteeger C, et al: Brain oxygen tension in severe head injury. **Neurosurgery 46:**868-76, 2000

389. Van der Linden P, De Hert S, Belisle S, De Groote F, Mathieu N, d'Eugenio S, et al: Comparative effects of red blood cell transfusion and increasing blood flow on tissue oxygenation in oxygen supply-dependent conditions. **Am J Respir Crit Care Med 163:**1605-1608, 2001

390. van Dongen KJ, Braakman R, Gelpke GJ: The prognostic value of computerized tomography in comatose head-injured patients. **J Neurosurg 59:**951-957, 1983

391. van Santbrink H, Maas AI, Avezaat CJ: Continuous monitoring of partial pressure of brain tissue oxygen in patients with severe head injury. **Neurosurgery 38:**21-31, 1996

392. van Santbrink H, Schouten JW, Steyerberg EW, Avezaat CJ, Maas AI: Serial transcranial doppler measurements in traumatic brain injury with special focus on the early posttraumatic period. **Acta Neurochir (Wien) 144:**1141-1149, 2002

393. van Santbrink H, vd Brink WA, Steyerberg EW, Carmona Suazo JA, Avezaat CJ, Maas AI: Brain tissue oxygen response in severe traumatic brain injury. **Acta Neurochir (Wien) 145:**429-38, 2003

394. Vavilala MS: Cerebral oximetry: Patience is a virtue but not a virtue for the patient, yet? **Pediatr Crit Care Med 8:**192-193, 2007

395. Vavilala MS, Bowen A, Lam AM, Uffman JC, Powell J, Winn HR, et al: Blood pressure and outcome after severe pediatric traumatic brain injury. **J Trauma 55:**1039-1044, 2003

396. Vavilala MS, Kincaid MS, Muangman SL, Suz P, Rozet I, Lam AM: Gender differences in cerebral blood flow velocity and autoregulation between the anterior and posterior circulations in healthy children. **Pediatr Res 58:**574-578, 2005

397. Vavilala MS, Lee LA, Boddu K, Visco E, Newell DW, Zimmerman JJ, et al: Cerebral autoregulation in pediatric traumatic brain injury. **Pediatr Crit Care Med 5:**257-263, 2004

398. Vavilala MS, Muangman S, Tontisirin N, Fisk D, Roscigno C, Mitchell P, et al: Impaired cerebral autoregulation and 6-month outcome in children with severe traumatic brain injury: Preliminary findings. **Dev Neurosci 28:**348-353, 2006

399. Vavilala MS, Tontisirin N, Udomphorn Y, Armstead W, Zimmerman JJ, Chesnut R, et al: Hemispheric differences in cerebral autoregulation in children with moderate and severe traumatic brain injury. **Neurocrit Care Dec 13** E-Pub. , 2007

400. Vereczki V, Martin E, Rosenthal RE, Hof PR, Hoffman GE, Fiskum G: Normoxic resuscitation after cardiac arrest protects against hippocampal oxidative stress, metabolic dysfunction, and neuronal death. **J Cereb Blood Flow Metab 26:**821-835, 2006

401. Vespa P, Bergsneider M, Hattori N, Wu HM, Huang SC, Martin NA, et al: Metabolic crisis without brain ischemia is common after traumatic brain injury: A combined microdialysis and positron emission tomography study. **J Cereb Blood Flow Metab 25:**763-774, 2005

402. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, et al: Anemia and blood transfusion in critically ill patients. **JAMA 288:**1499-1507, 2002

403. Vincent JL, Piagnerelli M: Transfusion in the intensive care unit. **Crit Care Med 34:**S96-101, 2006

404. Voulgaris SG, Partheni M, Kaliora H, Haftouras N, Pessach IS, Polyzoidis KS: Early cerebral monitoring using the transcranial doppler pulsatility index in patients with severe brain trauma. **Med Sci Monit 11:**CR49-52, 2005

405. Wahlstrom MR, Olivecrona M, Koskinen LO, Rydenhag B, Naredi S: Severe traumatic brain injury in pediatric patients: Treatment and outcome using an intracranial pressure targeted therapy - the Lund concept. **Intensive Care Med 31**:832-839, 2005

406. Walsh TS, McArdle F, McLellan SA, Maciver C, Maginnis M, Prescott RJ, et al: Does the storage time of transfused red blood cells influence regional or global indexes of tissue oxygenation in anemic critically ill patients? **Crit Care Med 32**:364-371, 2004

407. Wartenberg KE, Mayer SA: Multimodal brain monitoring in the neurological intensive care unit: Where does continuous EEG fit in? **J Clin Neurophysiol 22**:124-127, 2005

408. Wartenberg KE, Schmidt JM, Mayer SA: Multimodality monitoring in neurocritical care. **Crit Care Clin 23**:507-538, 2007

409. Weiskopf RB, Feiner J, Hopf H, Lieberman J, Finlay HE, Quah C, et al: Fresh blood and aged stored blood are equally efficacious in immediately reversing anemia-induced brain oxygenation deficits in humans. **Anesthesiology 104**:911-920, 2006

410. Weiskopf RB, Viele MK, Feiner J, Kelley S, Lieberman J, Noorani M, et al: Human cardiovascular and metabolic response to acute, severe isovolemic anemia. **JAMA 279**:217-221, 1998

411. Wesson DE, Williams JI, Spence LJ, Filler RM, Armstrong PF, Pearl RH: Functional outcome in pediatric trauma. **J Trauma 29**:589-592, 1989

412. White JR, Farukhi Z, Bull C, Christensen J, Gordon T, Paidas C, et al: Predictors of outcome in severely head-injured children. **Crit Care Med 29**:534-540, 2001

413. Yager JY, Thornhill JA: The effect of age on susceptibility to hypoxic-ischemic brain damage. **Neurosci Biobehav Rev 21**:167-174, 1997

414. Yeung JH, Chang AL, Ho W, So FL, Graham CA, Cheng B, et al: High risk trauma in older adults in Hong Kong: A multicentre study. **Injury 39**:1034-1041, 2008

415. Zauner A, Bullock R, Di X, Young HF: Brain oxygen, CO2, pH, and temperature monitoring: Evaluation in the feline brain. **Neurosurgery 37**:1168-76, 1995

416. Zauner A, Daugherty WP, Bullock MR, Warner DS: Brain oxygenation and energy metabolism: Part I - Biological function and pathophysiology. **Neurosurgery 51:**289-301, 2002

417. Zauner A, Doppenberg EM, Woodward JJ, Choi SC, Young HF, Bullock R: Continuous monitoring of cerebral substrate delivery and clearance: Initial experience in 24 patients with severe acute brain injuries. **Neurosurgery 41:**1082-91, 1997

418. Zgleszewski SE, Zurakowski D, Fontaine PJ, D'Angelo M, Mason KP: Is propofol a safe alternative to pentobarbital for sedation during pediatric diagnostic CT? **Radiology 247:**528-534, 2008

419. Zubkov AY, Lewis AI, Raila FA, Zhang J, Parent AD: Risk factors for the development of post-traumatic cerebral vasospasm. **Surg Neurol 53:**126-130, 2000

420. Zwienenberg M, Muizelaar JP: Severe pediatric head injury: The role of hyperemia revisited. **J Neurotrauma 16:**937-943, 1999