Paediatric Traumatic Brain Injury: The Relationship between Intracranial Pressure and Brain Oxygenation

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DECLARATION

I, Ursula Karin Rohlwink (RHLURS001), hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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A word of thanks

Embedded in the lines of this thesis is the tremendous support of a number of special individuals, to whom I am deeply grateful.

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Abstract

Introduction: Intracranial pressure (ICP) monitoring is a cornerstone of care for patients with severe traumatic brain injury (TBI). The primary goal of ICP treatment is to preserve brain oxygenation, and since brain oxygenation is usually not measured, the control of ICP is used as a surrogate marker. However studies indicating that cerebral hypoxia/ischemia may occur in the face of adequate ICP and cerebral perfusion pressure (CPP) suggest that the interaction between ICP and brain oxygenation is poorly understood and warrants further investigation. This is of particular importance in the context of children in whom the interpretation of relationships between intracranial factors is even more complex due to changing physiological norms with age. To date little scientific data exists in children and treatment threshold values are often extrapolated from adult guidelines.

This study aims to better understand the relationship between ICP and brain oxygenation measured as brain tissue oxygen tension (PbtO2) in a large paediatric cohort suffering from severe TBI. Specifically analysis 1) investigated ICP and PbtO2 profiles over time following TBI, 2) examined the relationship between ICP and PbtO2 from time-linked paired observations, 3) explored various critical thresholds for ICP and PbtO2, and 4) interrogated digital data trends depicting the relationship between ICP and PbtO2. The level of agreement between hourly recorded and high frequency electronic data for ICP and PbtO2 was also evaluated.

Method: Paired ICP and PbtO2 data from 75 children with severe TBI were tested with correlation and regression. Additional analyses controlled for mean arterial pressure (MAP), arterial partial pressure of oxygen (PaO2), CPP, arterial partial pressure of carbon dioxide (PaCO2) and haemoglobin (Hb) using multivariate logistic regression analysis and general estimating equations. Various thresholds for ICP were examined; these included age-related thresholds to account for the potential influence of age. Receiver-operating curves (ROCs) were used to graphically demonstrate the relationships between various thresholds of ICP and various definitions of low PbtO2. These were constructed for pooled and individual patient data. Interrogation of electronically recorded data allowed for case illustrations examining the relationship between ICP and PbtO2 at selected time points. Hourly and electronic data were compared using Bland and Altman plots and by contrasting the frequency of ICP and PbtO2 perturbations recorded with each system.

Result: Analyses using over 8300 hours of paired observations revealed a weak relationship between ICP and PbtO2, with an initially positive but weak slope ($r = 0.05$) that trended downwards only at higher values of ICP. Controlling for inter-individual differences, as well as MAP, CPP, PaO2, PaCO2 and Hb did not strengthen this association. This poor relationship was further reflected in the examination of threshold ICP values with ROCs, no singular critical ICP threshold for compromised brain oxygenation was discernible. Using age-based thresholds did not improve this relationship and individual patient ROCs demonstrated inter-individual heterogeneity in the relationship between ICP and PbtO2. However, it was clear that in individual patients ICP did exhibit a strong negative relationship with PbtO2 at particular time points, but various different relationships between the 2 variables were also demonstrated. A high level of agreement was found between hourly and electronic data.

Conclusion: These results suggest that the relationship between ICP and PbtO2 is highly complex. Although the relationship in individual children at specific time points may be strong, pooled data for the entire cohort of patients, and even for individual patients, suggest only a weak relationship. This is likely because several other factors affect PbtO2 outside of ICP, and some factors affect both independently of each other. These results suggest that more study should be directed at optimising ICP thresholds for treatment in children. The use of complimentary monitoring modalities may assist in this task. Depending on the adequacy of measures of brain perfusion, metabolism or oxygenation, it is possible that targeting a range of ICP values in individual patients may be appropriate; however this would require detailed investigation.

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Abbreviations

BP	Blood Pressure
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CSF	Cerebrospinal fluid
CPP	Cerebral perfusion pressure
DC	Decompressive craniectomy
FiO2	Inspired fraction of oxygen
GCS	Glasgow coma scale
GEE	General estimating equation
Hb	Haemoglobin
ICP	Intracranial pressure
IQR	Interquartile range
MAP	Mean arterial pressure
Mdn	Median
MVA	Motor vehicle accident
Na	Sodium
PaO2	Partial pressure of arterial oxygen
PaCO2	Partial pressure of arterial carbon dioxide
PbtO2	Brain tissue oxygen tension
pAR	Pressure autoregulation
ROC	Receiver operating curve
SaO2	Pulse oximetry
SBP	Systolic blood pressure
SjvO2	Jugular venous saturation
TBI	Traumatic brain injury
TCD	Transcranial Doppler

Chapter 1

TRAUMATIC BRAIN INJURY IN CHILDREN: A BRIEF EPIDEMIOLOGICAL OUTLINE

Background

Traumatic brain injury (TBI) is a major contributor to the burden of disease in children and adults worldwide [82, 98, 110]. In the United States (US) injury is the leading cause of death in patients from ages 1 to 34 years [9, 116] and accounts for more than two thirds of deaths in children between the ages of 5 and 19 years [1], with nearly 3000 children dying of TBI each year [33]. In developing countries the impact of TBI is more concerning; in South Africa for example, injury remains the leading cause of death in children over the age of 4 years [15], and the chances of dying due to injury in childhood is 6 times greater than in the Unites States [15, 77]. Of all injured children, the highest risk of death and permanent disability occurs in those who sustain an injury to the head [21, 73, 129].

Outcome

Mortality rates reported in paediatric studies of TBI range from 20-30%. Many of these deaths are potentially preventable [38] and the high incidence of death and neurological disability associated with TBI may be attenuated by effective medical care. Early access to efficient emergency care alone may decrease paediatric deaths by as much as 30% [22] and improved outcome is associated with more vigorous in-hospital management [125, 136]. Most of this treatment is directed at preventing or ameliorating secondary insults associated with TBI.

Severe TBI has a significant impact on the lives of those children affected, not only in terms of the high mortality, but also because of the potential for permanent neurological, physical and cognitive disability in survivors. TBI presents many challenges for the child affected, their family, schools and society at large. Children who have incurred an injury to the head may experience considerable cognitive and behavioural deficits which have far reaching consequences and may persist for life. Memory impairment, learning difficulties, speech and communication difficulties are among the most common cognitive impairments and behavioural problems associated with poor control over negative emotions may also arise [112]. Management of these unique challenges requires the development and availability of

specialized education and rehabilitation programs, which would ideally provide for the education and support needs of the family as well [112]. Currently the economics of health care render such services limited, and poor outcome associated with TBI continues to have significant economic implications on the health care system. TBI accounts for an annual incidence of hospitalisation of 85 per 100 000 and 235 per 100 000 in the US and Europe respectively, it poses one of the largest financial burdens on medical expenses and the indirect costs of years of life lost due to disability and death are great [82, 109, 118, 130].

Demographic Profiles of Paediatric TBI

Boys sustain TBI more commonly than girls. The mechanism of injury differs according to age and economic background and is associated with different levels of injury severity and pathology [47]. Mild TBI is often the result of minor falls, whereas severe TBI is more commonly caused by falls from a significant height and motor vehicle accidents (MVA). Severe TBI in infants is often inflicted, associated with severe diffuse injury and a high prevalence of ischemic injury due to a delay in treatment. Falls are the most common cause of TBI among toddlers, while older children are more likely to incur injury through MVA's. Diffuse injury is common in children, with focal contusions and haematomas seen less frequently than in the adult population [47].

Studies investigating paediatric TBI differ in terms of the age range with which they define childhood [26, 52, 67, 111, 131] with some studies including patients up to the age of 18 -21 years [25, 52]. Age range is an important consideration when studying a paediatric population as children of differing ages display variation in their physiology, their vulnerability and sensitivity to injury, and their recovery trajectories. Age-related differences exist in intracranial pressure (ICP) and blood pressure (BP) norms within the pediatric population, with normal values of ICP and BP rising with age [27, 115]. Mortality is highest in the very young, decreasing till the age of 12, after which it begins to rise again [27]. The physiological makeup of adolescents may also have greater similarity to adults than is the case for younger children. This has significant bearing on treatment thresholds and the extent to which these management guidelines should be extrapolated from adult values. This dissertation employs a paediatric age range from 0-14 years.

Assessing children in comparison to adults

Children are different to adults in several important aspects relevant to TBI. Children and adults are vulnerable to different kinds of injury mechanisms, injury type and biomechanics. In the physiological domain, they exhibit substantial differences in normative ranges for BP,

cerebral blood flow (CBF) and ICP, as well as differences in pressure-volume intracranial dynamics and possibly autoregulatory mechanisms. The pathophysiological cascade following TBI may vary significantly with age, and consequently also the mode of optimal treatment. For example, medications like anticonvulsants may have unique effects on the immature nervous system, and measures such as decompressive craniectomies (DC) may have more beneficial outcomes in the paediatric population [47]. The extrapolation of treatment guidelines from adult research is therefore not entirely appropriate, but often occurs because of the lack of data for the paediatric population. While the developing brain may hold the advantage of greater plasticity, it is also apparent that it is simultaneously more vulnerable to injury. Consequently, children may differ significantly in their recovery trajectories and in the long term neurocognitive consequences of their injury [47, 64].

Chapter 2

SECONDARY INJURY: CEREBRAL ISCHEMIA

Primary and Secondary Injury

Primary injury following TBI involves the cerebral tissue damage that occurs at the moment of injury. Little can be done to amend this damage by medical intervention, and consequently the window of opportunity lies in the time following the trauma as attempts are made to avoid and ameliorate secondary injury.

Secondary injury is the delayed loss of viable tissue attributable to events set in motion at the time of primary injury or its aftermath. Secondary brain injury plays a major role in determining outcome after TBI, and avoidable factors may contribute to as much as 42% of TBI deaths in children [37, 118]. Secondary insults associated with TBI may manifest in terms of intracranial dynamics, like intracranial hypertension and seizures, systemic dynamics including hypotension and hypoxia, as well as cellular dynamics, including mitochondrial dysfunction, neurotransmitter release and cell damage [82]. Understanding and treating these secondary insults appropriately is crucial as timely intervention may improve outcome.

Cerebral Ischemia/ Hypoxia

The mechanisms of secondary injury are diverse, however the final common pathway is often cerebral ischemia [139]. Cerebral ischemia is a common and potentially devastating secondary injury following TBI. It represents a major cause of mortality and morbidity in these patients and post-mortem studies suggest that more than 90% of patients who die due to TBI have evidence of cerebral ischemic damage [49]. Prompt detection and treatment of ischemia may minimize the potential for irreversible brain damage [55].

Adequate oxygenation of the brain depends on several factors, including sufficient systemic oxygen delivery, perfusion of the brain, and diffusion of oxygen through the tissues. There are several physiological factors that in turn affect each of these parameters.

Cerebral blood flow

Reduced CBF occurs commonly during the acute stages after TBI [7 14 140]. Under normal circumstances CBF and cerebral metabolism are tightly coupled. Normal values of CBF range between 45 and 60 ml/100g/min (average for gray and white matter) and the ischemic

threshold is estimated at 18 ml/100g/min [10 90 121 146]. A reduction of CBF levels below this critical threshold is associated with corresponding changes in cerebral metabolism [119] including progressive electrical failure, EEG flattening, as well as cellular acidosis and net energy loss resulting from an imbalance of increasing glycolysis and limited oxidative phosphorylation. Further decreases in CBF result in membrane failure, and ultimately infarction, as CBF falls below 10 ml/100g/min [90]. The extent of ischemic damage is dependent on both the depth and duration of tissue hypoxia.

However, in the head-injured patient the relationship between CBF and metabolism is more complex. Lower levels of CBF may not necessarily equate to ischemia and may be appropriate for injured tissue that has reduced metabolic needs and/or mitochondrial dysfunction. Conversely, supposedly normal levels of CBF may not be adequate where there is increased metabolic demand if there is uncoupling between CBF and cerebral metabolism. Metabolic needs after head injury, mitochondrial dysfunction, level of oxygen extraction and coupling between metabolism and CBF must therefore be taken into account to correctly interpret absolute values of CBF [32].

Cerebral perfusion pressure

CBF depends on several factors, including cerebral perfusion pressure (CPP). CPP plays an important role in the pathophysiological cascade leading up to ischemia; first, it represents the pressure gradient across the cerebrovascular bed and is therefore an important regulator of CBF, and second, CPP contributes to the intravascular hydrostatic pressure, and can be an important determinant of oedema formation [55]. When CPP is reduced below the lower threshold of autoregulation (40-50mm Hg), CBF proportionately decreases as the autoregulatory capacity is exhausted [78, 99 31, 61] potentiating the development of cerebral ischemia, depending on the duration of the insult.

CPP is the difference between mean arterial pressure (MAP) and ICP (CPP = MAP – ICP), and therefore, reductions in CPP are seen either due to decreased MAP or increased ICP, however it is suggested that the former has the greater negative effect [55]. CPP is largely dependent on the status of cerebral pressure autoregulation, and consequently has implications for ICP and brain oxygenation management.

Ensuring adequate brain perfusion is important in attempting to prevent ischemic episodes, however setting an optimal CPP is a matter of debate in both adult and child health care. In children the task is further complicated by age-related variation in BP and autoregulation profiles. Studies done in children have found differing threshold values for outcome

prediction [26, 28, 52, 67, 101, 142]. Perhaps ideally CPP management should be tailored to the physiological, pathological and age profile of the individual patient but there is little data to support this as yet.

Pressure Autoregulation

Normal cerebral functioning is highly dependent on the maintenance of constant CBF. The impact of fluctuations in MAP on cerebral perfusion is therefore tightly controlled by pressure autoregulation and the vascular reactivity of cerebral resistance vessels (arterioles of approximately 200 micron in diameter) [72].

When pressure autoregulation is intact, an increase in MAP within the autoregulatory range will result in cerebral vasoconstriction and maintenance of a relatively constant CBF. Conversely, cerebral vessels respond to a drop in MAP by vasodilatation allowing for increased flow. However, when pressure autoregulation is impaired cerebral vessels fail to adjust their calibre to changes in MAP and passively distend with increased blood pressures, causing increased CBV and therefore increased ICP. Clinically, the changes in ICP in response to a change in blood pressure may be helpful as a surrogate marker of the status of autoregulation [124] .

Oxygen diffusion through tissues

In addition to limited perfusion, structural mechanisms relating to tissue damage may also cause cerebral ischemia. Transport of oxygen from the vessels into tissues takes place through diffusion, driven by partial pressure gradients. Consequently, increases in the diffusion distance of oxygen between the vessels and tissues may reduce intracellular oxygen tension and potentiate ischemia. Factors associated with TBI which may increase the diffusion distance include cytotoxic cell swelling, perivascular oedema, collapsed capillaries and arteriovenous shunting [92].

Managing secondary injury

TBI management focussed on averting secondary ischemic injury therefore must ensure that CBF and oxygenation are sufficient to meet cerebral metabolic needs. The pathophysiological cascade following TBI is complex, and this treatment end point involves managing the interplay of a number of relevant variables; ICP and brain oxygenation are fundamental among these, and form the basis of study in this dissertation.

Detecting secondary injury, or predicting which patients are at risk of developing secondary injury, remains a major challenge. Clinical assessment of neurological function can be challenging in patients who are sedated and artificially ventilated, currently used biomarkers of brain injury do not have sufficient sensitivity and specificity to warrant routine use to guide TBI care, and imaging of the brain does not necessarily predict who is at risk for secondary injury. Due to the limitations of these modalities, there has been increased interest in technologies that are able to monitor brain physiology and function continuously in the acute phase after TBI.

ICP and CPP monitoring have become a cornerstone of TBI care. Positron emission tomography (PET) imaging is currently the gold standard for detecting cerebral ischemia; however, these studies are primarily research tools, require stable patients, and can only determine the prevalence of ischemia at one point in time, whereas TBI is a dynamic pathophysiological process. Recent technology in the form of brain tissue oxygen tension (PbtO2) monitoring has allowed for a more direct means of assessing brain oxygenation and is being used increasingly in the management of patients with severe TBI [24, 46, 62, 65, 69, 75].

Chapter 3

INTRACRANIAL PRESSURE

ICP is elevated in 30-80% of head injured patients [105, 117]. Uncontrolled ICP is associated with considerable risk of herniation and brain ischemia, and is considered the major contributor to hospital death due to head injury [102].

Intracranial pressure physiology

According to the Monroe-Kellie doctrine the intracranial compartments coexist in a reciprocal manner, whereby small increases in the volume of any of the components can be offset by an equal, compensatory decrease in cerebrospinal fluid (CSF) volume and cerebral blood volume. This compliance allows for change in the intracranial volume which reflects only minimally on ICP. The cerebral compensatory reserve is however limited, and when the compensatory capacity is exhausted, any additional increases in intracranial volume may lead to a precipitous increase in ICP (Figure 1). This is reflected in the hyperbolic nature of the cranial pressure – volume relationship [108], with compliance being represented by change in volume /change in pressure. The nature of the pressure-volume curve may however demonstrate differences across time and across individual patients.

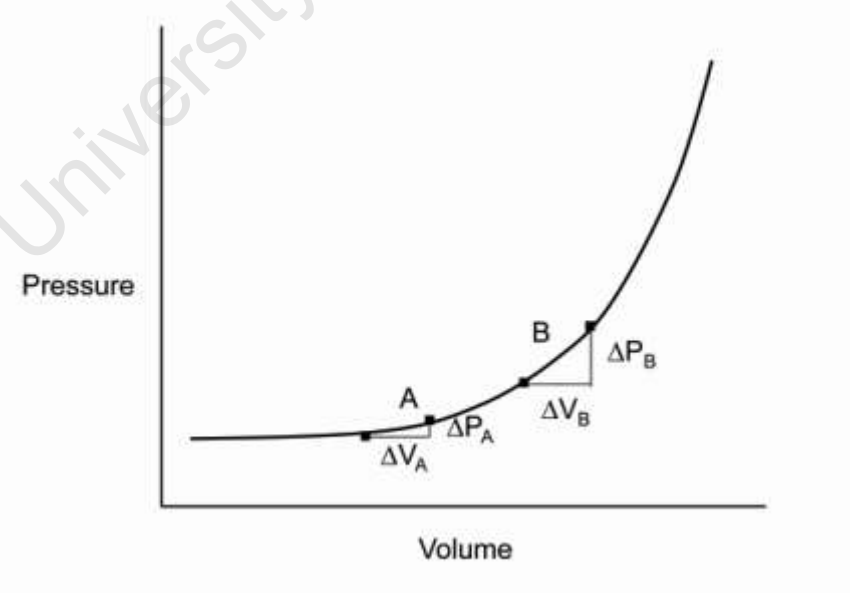


Figure 1: A graphic illustration of the pressure-volume curve of the brain. When compliance is greater (A), a given change in volume (ΔV_A) produces minimal change in ICP (ΔP_A). However, when compliance is decreased (B), the same change in volume (ΔV_B) produces a more significant increase in ICP (ΔP_B).

Factors affecting ICP

Several cerebral hemodynamic and regulatory mechanisms have important relationships with ICP. Blood pressure has a complex interaction with ICP. When pressure autoregulation is preserved, increasing BP within the normal autoregulatory range leads to active vasoconstriction of arterioles and an overall reduction in CBV, which leads to a slight decrease in ICP [45]. However, when autoregulation is impaired, increased BP passively distends the cerebral vessels causing increased CBV and ICP [13, 74]. The increase in BP may also increase intracapillary hydrostatic pressure, and potentially aggravate vasogenic oedema.

CO2 reactivity exerts a significant influence on ICP based on its effect on vascular tone and blood volume, whereby higher CO2 values are associated with vasodilation and hence increased ICP, and lower values with the reverse. Hyperventilation is therefore a commonly used and effective means of treating raised ICP, albeit with an increased risk of ischemia [97]. CBF and cerebral metabolism normally exhibit close coupling. In this way metabolic suppression may reduce ICP by reducing CBF, if coupling between CBF and metabolism is intact.

Intracranial hypertension following TBI

Raised ICP after TBI is an important manifestation of underlying physiological perturbations which may result in potentially dangerous changes to intracranial volume. These include; 1) traumatic hematomas in the intracerebral, subarachnoid, subdural or extradural spaces that may result in brain shifts, 2) cerebral oedema which contributes increased water to the intracranial volume due to cytotoxic or vasogenic mechanisms [88], and 3) changes in CBV as a result of impaired pressure autoregulation and the uncoupling between CBF and metabolism which may potentiate vascular congestion. Of note, hyperaemia was long thought to be a common cause of raised ICP in paediatric TBI, but is now considered to be less so [19, 148]. Post-traumatic hydrocephalus is less frequently encountered.

Consequences of raised ICP

Raised ICP may compromise brain oxygenation and cause herniation due to pressure gradients created within the cranial cavity [76, 144]. Brain oxygenation decreases as cerebral perfusion compromise leads to progressively reduced CBF and subsequent metabolic dysfunction associated with reduced CBF (especially below 18mls/100g/min).

Herniation is usually seen only with very high values of ICP, but may also occur at lower elevations of ICP than would be expected. Still, it is generally the adverse effects of ICP on brain perfusion and brain oxygenation that are of usual concern during ongoing patient management in the typical range of increased ICP managed in the ICU. The purpose of controlling ICP is therefore to ensure adequate CPP and CBF, thereby ensuring sufficient brain oxygenation and metabolic substrate delivery, while avoiding herniation [3, 64].

Time course of raised ICP

The time course of ICP after TBI is variable, and may be a function of the underlying cause of increased ICP. Intracranial hypertension may often develop in the acute stages following TBI due to haematomas, but may also have delayed onset due to progressive brain oedema [71, 98, 135]. In a study by Stocchetti et al [128] mean ICP rose progressively in the days following TBI, suggesting that continued monitoring is indicated by the continued occurrence of high ICP. In their cohort as much as 20% of patients demonstrated their highest mean ICP after Day 5. These findings are mirrored by those of Unterberg et al [135] who found delayed onset of intracranial hypertension in 31% of their patients, and O'Phelan et al [98] who found delayed ICP rise in 17% of their patients. However, all of these studies demonstrated the majority of ICP peaks early, within the first 72 hours, and suggest that delayed elevation in ICP may be attributable to delayed intracranial haemorrhage or delayed cerebral oedema surrounding contusions. The temporal heterogeneity in ICP also highlights intra- and inter-individual variability in TBI.

Methods of ICP monitoring

The external ventricular drain (EVD) is considered the gold standard for measuring ICP. It is associated with a low risk of infection and is thought to be the most accurate, inexpensive and reliable method. Intraparenchymal fibreoptic and electronic strain gauge systems are being used more frequently, especially where insertion of an EVD is complicated by small ventricle size. Subdural and extradural monitors may also be used although they are much less reliable than intraparenchymal monitors [80] [11]. Common to all of these parenchymal monitors is the issue of zero and sensitivity drift, which reduces the accuracy over time. However, most current monitors in use have relatively low rates of measurement drift.

The most common complications associated with ICP monitor insertion are haemorrhage, infection and device malfunction. In general the risk of these complications remains low [100], however the incidence may vary depending on the device used, the duration of monitoring and the insertion technique [11].

Managing ICP

Evidence indicates that raised ICP is associated with poor neurological outcome and increased mortality in children [3, 21, 25, 26, 64, 100, 110]. Although the evidence base for directing ICP monitoring and treatment in children is small it is clear that ICP monitoring and aggressive treatment to control intracranial hypertension are associated with improved clinical outcome [3, 39, 110]. The indications for ICP monitoring are however not well defined and current recommendations are extrapolated from adult guidelines [3]. Currently there is also only one set of international guidelines for treating ICP in severe paediatric TBI, however the poor quality of evidence available for establishing these guidelines has been highlighted by the authors [2, 6]. The currently recommended ICP treatment threshold for children is 20 mmHg [4, 93].

As yet no age-related threshold recommendations have been established, and none are recommended in the current guidelines, but a study conducted in paediatric ICU's across the United Kingdom found that most treating clinicians attempted to take account of age when setting ICP thresholds, although strategies were variable due to the lack of standard recommendations [115]. This finding is confirmed by a study of physician agreement on ICP treatment protocols, in which physician practice portrayed the greatest discrepancy with respect to age appropriate ICP thresholds [33]. It is apparent that international guidelines incorporating the unique physiological and pathophysiological profiles of children are needed, and would be of tremendous benefit in the treatment of these patients. To date there is still a paucity of research in this area.

Chapter 4

BRAIN OXYGENATION

Several techniques are available for monitoring various aspects of brain oxygenation, including 'snapshot' imaging of the brain, and continuous methods such as jugular venous bulb saturation (SjvO2), brain tissue oxygen tension (PbtO2) and near-infrared spectroscopy. These continuous monitors differ in the physiological variables they measure and the physical principles used to measure them. Arguably, PbtO2 appears to capture regional episodes of ischemia with greater accuracy, has an excellent time of good quality data with few artefacts [50] [70], and has tended to be favoured in the recent literature on neurocritical care management of TBI, subarachnoid haemorrhage, meningitis, and during cerebral surgery [24, 46, 62, 65, 69, 75]. It is considered to be a useful guide to clinical management [16, 41, 43, 44, 75, 107, 125] and a tool by which to explore the mechanisms of tissue oxygenation in the injured brain [92, 107]. A phase II trial is currently being planned in preparation for a Phase III randomised control trial assessing the effect of PbtO2 monitoring in severe TBI management.

Defining PbtO2

The matter of defining what exactly PbtO2 monitors measure is debated. It has been suggested that PbtO2 represents the balance between cerebral oxygen supply and demand, that it is associated with CBF [63, 137], that it represents the product of blood flow and arteriovenous difference in oxygen tension [107], and that it is associated with the mean transit time of blood through the brain [53], arteriovenous difference of oxygen, and end-capillary venous PO2 [43, 51, 107, 113]. This uncertainty may result from the fact that the specific determinants of PbtO2 are not yet well indentified, and aspects of oxygen diffusion in brain tissue are only beginning to be elucidated [92]. However, PbtO2 is probably best considered as a measure of the factors that affect both the perfusion and diffusion characteristics of oxygen in brain tissue.

Factors influencing PbtO2

Understanding the role of PbtO2 in the pathophysiology of TBI rests heavily on the appreciation that PbtO2 is a highly dynamic variable, significantly affected by a number of factors. A systemic factor which has a particularly important association with PbtO2 is the arterial partial pressure of oxygen (PaO2) since PbtO2 is a measure of the partial pressure of

oxygen in brain tissue. Therefore, even if blood is near full saturation, an increase in PaO2 will lead to an increase in PbtO2 although this may not necessarily reflect substantial changes in oxygen delivery or in cerebral metabolic rate of oxygen [107]. On the other hand, even when substantial changes to oxygen content have not occurred, higher partial pressures of oxygen may increase the gradient of oxygen diffusion into tissues. This may overcome barriers to diffusion resulting from tissue damage and oedema, which may increase the diffusion distance of oxygen[92], and in so doing improve metabolism [35, 83, 95, 132]. Arterial PCO2 may also influence PbtO2 as a consequence of the vasoreactive effects of PaCO2, if CO2 reactivity is preserved [50, 60, 85, 114]. Hypocarbia may lead to decreases in PbtO2 mediated by decreases in CBF, and hypercarbia may cause a rise in PbtO2 accompanied by an increase in CBF. On the other hand, very high levels of PaCO2 can also result in a substantial drop in PbtO2 as a marked increase in CBF may result in substantially increased CBV and subsequently ICP. Along with the different responses to CO2 in injured versus non-injured tissue, this may account for occasional 'paradox' reactions of PbtO2 to altered PaCO2 [50].

Studies that have examined the relationship between PbtO2 and CPP have shown conflicting results [8, 20, 31, 34, 66, 86, 104, 127, 134, 143]. While induced hypertension is usually associated with increased PbtO2, variability in PbtO2 responses may occur partly because of differences in the strength of autoregulation between patients. Increased ICP may cause a decrease in PbtO2 due to a local tissue pressure effect or by a reduction in CPP. However, the overall relationship between ICP and PbtO2 is variable because several other factors affect PbtO2 [44]. The relationship between ICP and PbtO2 will be discussed in greater detail in the following chapter.

Interpreting PbtO2 measurements

Normal and threshold values have not been established in healthy humans; however, animal studies demonstrating normal values in the region of 25-30 mmHg have been confirmed in patients with normal ICP and CPP, in normal tissue in patients with brain tumours, and in patients who underwent temporary clipping of cerebral vessels [34, 36, 57, 68, 70, 75, 81].

PbtO2 and outcome

Poor outcome following TBI has been shown to have a higher likelihood when PbtO2 levels fall progressively below 20 mmHg [136], reductions of less than 10 mmHg are typically associated with ischemic injury [113, 126] and a threshold of PbtO2 = 10mmHg appears to have the strongest association with outcome [16, 43, 75, 143]. Increased frequency, depth and duration of cerebral hypoxia are associated with poorer outcome [16, 29, 43, 126, 136, 138] and PbtO2 values

between 15 and 20 mmHg may act as an early warning sign for oligemia or cell damage [43]. PbtO2 levels less than 10 mmHg have been associated with classic ischemic CBF thresholds, jugular venous desaturation, perturbations in microdialysis parameters, decreased mitochondrial function and impaired neuronal activity [50, 54, 58, 113, 137]. Low PbtO2 values have been shown to be independent and strong prognosticators of poor outcome and death after adult and paediatric head trauma [43, 138]. In the largest study of paediatric TBI, PbtO2 was an independent factor associated with poor outcome, and a stronger predictor than other factors traditionally associated with outcome [43]. Furthermore, low PbtO2 was shown to be poorly predicted by commonly measured physiological and clinical factors such as ICP, CPP and systemic oxygenation [44].

Time course

Low PbtO2 values occur most commonly in the first 24 hours post-injury [29, 126, 138, 138], and correspond to lower CBF, increased lactate and cellular acidosis during this period [14, 30]. While low levels of PbtO2 may occur at any time during the acute phase, initially low PbtO2 appears to stabilize within 24 to 48 hours [141].

Methods of brain oxygenation monitoring

Three systems of measuring brain tissue oxygen tension have been developed commercially, the Licox (Integra Neurosciences, Plainsboro, NJ), the Neurotrend (Codman, Raynham, MA) which is no longer in use, and the newer Neurovent (Raumedic, Munchberg, Germany). The Licox is the current gold standard in PbtO2 measurement, and is used at our institution. It functions as a Clarke-type electrochemical probe composed of 2 metal coated electrodes placed in an oxygen permeable electrically insulating membrane. As they pass through the membrane oxygen molecules undergo reduction at the site of the measuring electrode, and the partial pressure of oxygen can therefore be measured by the voltage difference generated between the reference and measuring electrodes [120]. Complications associated with probe insertion are rare, and tissue damage is minimal [75]. The sampling area is approximately 13-14 mm^2 [59, 75, 103], considering that cerebral oxygen distribution may demonstrate significant spatial heterogeneity, this small penetration depth does limit the generalizability of probe readings, making this a more focal monitor.

The Neurovent is an optical probe which works on a different principle of dynamic luminescence quenching. On contact with oxygen molecules, the luminescent light emitted from a luminophore encapsulated in an oxygen permeable membrane is attenuated and the measurable luminescence signal decreases. The oxygen tissue measurements can be

calculated based on the relationship between the tissue oxygen concentration and the luminescence intensity and lifetime [59, 120]. The oxygen sensitive sampling area is approximately 22 mm² [59, 103] and the probe combines PbtO2 with ICP and brain temperature. While evidence suggests that the Neurotrend performs similarly to the Licox [59, 103], further research would be valuable in validating this new technique.

Managing PbtO2

SjvO2 and PbtO2 monitoring have been included in the Brain Trauma Foundation's guidelines for brain oxygenation monitoring for the first time at the level of an option that SjvO2 < 50% and PbtO2 < 15 mmHg represent treatment thresholds [16]. Due to a paucity of research in this field, no formal treatment guidelines are outlined for paediatric TBI. In adults however the currently used treatment threshold in many centres is 20 mmHg [84], but some centres treat at lower thresholds [136].

PbtO2-directed treatment

While it is clear that low PbtO2 is associated with poorer outcome [16, 43, 125, 136, 138], the issue of whether treatment directed by PbtO2 monitoring improves outcome needs further clarification, similar to all other monitors including ICP. Stiefel et al [125] compared PbtO2 directed-therapy with ICP-directed therapy and found that PbtO2-directed therapy led to a significant decrease in mortality. In a cohort of 139 patients with TBI Narotam et al [94] also reported decreased mortality associated with PbtO2 monitoring as well as significantly improved clinical outcomes in comparison to standard ICP/CPP-directed treatment. On the other hand, one study suggested that PbtO2-directed therapy did not benefit patients [91]. The finding of this study may however be limited by the fact that the indication for PbtO2 monitoring was not controlled and therefore the patient groups were not equal. Further study is required for Class I evidence demonstrating the benefit of PbtO2 monitoring. As in the case of ICP monitoring, a randomized trial of PbtO2 monitoring is needed. Clinical trials to compare ICP and PbtO2-directed treatment are in preparation.

Monitoring PbtO2

It is worth highlighting that PbtO2 is a focal monitor, and therefore careful thought should be given to placement of the catheter. Although 'normal' tissue may not display the perturbations of tissue at higher risk of ischemic injury, peri-contusional or peri-lesional tissue may exhibit abnormal physiology and responses to interventions that may not reflect the responses of the rest of the brain [34, 50, 66]. The current institutional practice at Red Cross

Children's Hospital is to place the catheter in right frontal white matter when there is diffuse injury, on the affected side of a more injured hemisphere, and in the normal-appearing tissue surrounding the contusion in the case of focal injury. There is much discussion about to what degree focally measured PbtO2 can be extrapolated to reflect a more global assessment of brain oxygenation. Significant spatial heterogeneity may limit the usefulness of data obtained from a single location. Additionally, because PbtO2 is not an 'ischemia monitor' per se [96], other factors that influence PbtO2, such as diffusion through tissues, must be considered in the interpretation of results.

Currently there are no formal guidelines detailing indications for PbtO2 monitoring in either adults or children.

Chapter 5

THE RELATIONSHIP BETWEEN INTRACRANIAL PRESSURE AND BRAIN OXYGENATION

The relationship between intracranial hypertension and brain oxygenation

Elevated ICP may compromise brain oxygenation in several ways. First, elevated ICP reduces CPP and thereby may compromise blood flow and oxygen delivery to the brain, depending on the presence of autoregulation and the absolute reduction in CPP. Second, high ICP may exert a tissue pressure effect which may further compromise tissue perfusion and oxygen diffusion into cells.

Physiologically, raised ICP and impaired brain oxygenation are related, in the absence of other influencing factors. The evidence base indicating the association between high ICP and poor outcome is extensive [17, 87, 89]. Many studies have also shown low brain oxygenation to be associated with ischemia, infarction and poor outcome [43, 126, 136, 138]. Patients who die after sustaining TBI often have evidence of both high ICP and brain ischemia. Therefore, a primary reason for treating ICP is to ensure adequate brain perfusion and prevent cerebral ischemia. However, several studies have shown that ischemic brain damage may occur despite adequate CPP and ICP. A summary of a number of studies investigating the relationship between ICP and PbtO2 are outlined below. To date, none have investigated this in children.

Investigating ICP and brain oxygenation

In a study on the prevalence of brain hypoxia and its relationship to ICP in adult TBI, Chang et al [29] found that hypoxic episodes occurred mostly in the context of normal ICP and only 23% occurred concurrently with episodes of ICP > 20 mmHg. Brain hypoxia exhibited a stronger association with CPP < 70 mmHg. On the other hand, Le Roux et al [79] found that elevated arteriovenous difference of oxygen was not significantly related to CPP. These results indicate that ischemia/ hypoxia may also occur despite apparently adequate levels of CPP and that this may be explained by other factors such as disturbed autoregulation.

Stiefel et al [126] assessed the role of adequate ICP and CPP in ensuring acceptable cerebral oxygenation after resuscitation in adult severe TBI. Even when the criteria for adequate resuscitation of ICP ≤ 25 mmHg and CPP ≥ 60 mmHg were achieved, one third of patients

still experienced PbtO2 < 10 mmHg within the first hour after resuscitation. Episodes of low PbtO2 were associated with poorer outcome, suggesting that cerebral hypoxia concurrent with normal ICP and CPP is an important factor leading to secondary brain injury. Similar findings were demonstrated in a paediatric study conducted by Figaji et al [41] in which adherence to guideline treatment targets of ICP < 20 mmHg and CPP > 50 mmHg was associated with low PbtO2 (< 10mmHg) in approximately one third of patients. Of note, in a separate paediatric study the association between ICP and poor outcome was reduced when PbtO2 was included in multivariate analysis [43].

Van den Brink et al [138] also found that PbtO2 was strongly associated with poor outcome, but PbtO2 values were not significantly associated with either high values of ICP of long duration (> 25 mmHg for ≥ 60 minutes) or low values of ICP. In a study using both SjvO2 and PbtO2, Gopinath et al [48] found that elevated ICP was responsible for less than 50% of cerebral ischemic episodes.

A number of these studies were limited by small sample sizes of less than 30 patients, but their results highlight important characteristics of low brain oxygenation and its relationship with ICP, suggesting that ICP seems to have a limited effect on PbtO2. While this may indeed reflect the general relationship for pooled data analysis between ICP and measures of brain oxygenation, it is important to note that ICP can have a very significant negative effect on PbtO2. This is clear, for example, in studies investigating the change in cerebral physiology subsequent to decompressive craniectomy (DC).

Ho et al [56] conducted a study on 16 TBI patients who underwent DC for refractory intracranial hypertension. Their results indicated a significant decrease in ICP accompanied by a significant increase in PbtO2 post-DC. In paediatric TBI, Figaji et al [40] assessed the changes in ICP and PbtO2 following DC for elevated refractory ICP. When pre- and postoperative values for ICP and PbtO2 were compared, there was a significant decrease in ICP from 40 ±14.9 mmHg to 17 ±9.02 mmHg after surgery. This was accompanied by a significantly increase in PbtO2 from 18 ±12.8 mmHg to 43±15.4 mmHg, that was sustained after the operation. These findings suggest that ICP and PbtO2 may demonstrate a closer relationship in individual patients.

Implications for treatment

Current TBI treatment emphasises controlling ICP as one of the principle strategies for averting secondary ischemic injury after TBI, predominantly as a means of ensuring adequate CPP [2, 18].While ICP directed treatment may improve outcome, substantial evidence

indicates that ischemic damage may occur under circumstances of 'normal' CPP and ICP. This may be due to several factors, including inappropriately low CBF, vasospasm, increased barriers to oxygen diffusion, subclinical seizures, or metabolic derangement. It is equally possible that the currently used threshold for treating ICP, especially in children, is not optimal; therefore, what is considered normal ICP is not what should be optimally targeted.

The relationship between ICP and brain oxygenation is poorly understood, but has important implications for treatment protocols, given that ICP has become a cornerstone of care, and that measures of brain oxygenation or perfusion are not commonly employed in the management of severe TBI. Treating at lower thresholds of ICP increases the risk of adverse effects associated with ICP-reducing therapies, and therefore over-treatment is not advisable. On the other hand, it is clear that ICP can have a marked effect on PbtO2 in some circumstances, which necessitates that significant elevations of ICP be treated. However, the level of ICP which would constitute a significant elevation is unclear, particularly in the paediatric context. Because there are dangers in both under-treating and over-treating ICP, and because the uncertainty of which ICP threshold to treat is greatest in children, a better understanding of the relationship between ICP and PbtO2 in children would be useful.

Chapter 6

STUDY AIMS

This study aimed to investigate the relationship between ICP and PbtO2 in depth for children with severe TBI. Consequently, analyses were conducted in a sequential manner, looking at the relationship first broadly, and then in increasingly defined and narrower analyses.

1. **To describe the profile of ICP and PbtO2 following TBI**

This analysis explored the profiles of ICP and PbtO2 following TBI by identifying the frequency of intracranial hypertension and low brain oxygenation as well as outlining their profile for the acute phase of monitoring post trauma. This described their trends in individual patients and across the cohort, and documented the time frames of highest ICP and lowest PbtO2. The purpose of this first analysis was to provide an overview of ICP and PbtO2 in this cohort of patients.

2. **To examine the time-linked relationship between ICP and PbtO2**

To investigate the direct relationship between ICP and PbtO2, analysis was conducted in a step wise fashion. The relationship was examined 1) using raw data of paired observations in pooled analysis, 2) controlling for variation between individuals, and 3) controlling for relevant systemic factors, namely MAP, CPP, PaO2, PCO2 and Hb.

3. **To explore critical thresholds for ICP and PbtO2**

This analysis aimed to examine key values of ICP in relationship to PbtO2 to explore whether critical ICP thresholds could be defined. Given the different thresholds of significance for PbtO2, these ICP values were examined against several thresholds of PbtO2 from 20mmHg to 5mmHg. Receiver-operating characteristic curves (ROCs) were constructed for each of these thresholds.

Since children may vary significantly from infancy to adolescence, age may potentially influence the point at which ICP negatively impacts on PbtO2. Therefore, age-related thresholds for ICP were investigated in 3 different age categories.

Since TBI may exhibit substantial inter-individual heterogeneity in the ICP and PbtO2 thresholds that may be tolerated, and because examination of data in a large cohort may

mask significant relationships seen in individual patients, additional ROCs for individual patients were constructed using hourly and electronic data.

4. To illustrate relationships between ICP and PbtO2 in individual cases

Values in PbtO2 and ICP may pass critical levels progressively and transiently; when averaged, these differences may be camouflaged [37]. Therefore, it is possible that the relationship between ICP and PbtO2 values when averaged over a large cohort like in this study, or even over a long time period in a single patient, may appear weak. However, the association between ICP and PbtO2 may be very significant within an individual patient at particular time points. Electronic data trends for individual patients were reviewed to find examples of the dynamic relationship between ICP and PbtO2.

5. Data Capturing

Data used for this analysis was predominantly extracted from hourly recordings taken during the monitored period in the ICU, and is the method by which data are commonly recorded and analysed in many studies However, large variation in physiological variables may occur in the space of one hour and may represent important physiological events. Continuously recorded data provides an uninterrupted complete account of physiological progress while hourly recordings provide a snapshot of the physiological state of the brain. Hourly data was therefore compared with high frequency collection of electronic data available (data points averaged over 10 second periods) to examine whether a substantial difference exists in the methods of data collection, and if this result could inform future study options.

Chapter 7

METHODS

Patient Selection

Data collection for this project continued as part of an ongoing record of paediatric TBI data started in June 2006. Data were collected prospectively for paediatric patients admitted to Red Cross War Memorial Children's Hospital who underwent ICP and PbtO2 monitoring for severe TBI (postresuscitation Glasgow Coma Score [GCS] of ≤ 8). All patients included were under the age of 15 years, in keeping with hospital policy.

Indications for intracranial monitoring involved a postresuscitation GCS of ≤ 8 or deterioration to this level after admission. Monitoring was not considered for rapidly waking patients for whom early extubation was likely, if 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). Some patients were not monitored because PbtO2 catheters were not available or all the monitoring machines were in use. ICP and PbtO2 catheters were placed in an ipsilateral location in close proximity to each other. Informed consent was obtained from all parents before insertion of intracranial monitors.

Resuscitation followed the Paediatric Advanced Trauma Life Support guidelines, patients underwent endotracheal intubation, had a CT head scan, and were mechanically ventilated in the paediatric intensive care unit (ICU).

Data Collection

Data was collected manually from patient clinical folders. With the recent addition of a computerised physiologic recording system, ICMPlus® (University of Cambridge, U.K), electronic data for physiological variables of the last 16 patients were also recorded.

Admission Clinical and Demographic Data

General Data

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

Classification and Grading Systems

The postresuscitation GCS score of each patient was recorded, and the motor component separately documented. The Paediatric Coma Scale was used for preverbal children [122, 123].

Postresuscitation pupillary reactions were categorised as bilaterally reactive, unilaterally nonreactive, or bilaterally nonreactive. The influence of medications was excluded.

Time sequence

The following were also recorded: time of admission (after injury), time of monitor insertion (time from injury to monitor insertion), duration of monitoring, and length of stay in the ICU.

Physiological Data

Intracranial monitors were inserted as early as possible after admission to the ICU and monitoring continued until both ICP and PbtO2 were considered stable for > 48 hours, or until the patient died. Measures of ICP, CPP, PbtO2, core and brain temperature, saturation, as well as the ventilator inspired fraction of oxygen (FiO2) were recorded on an hourly basis as part of standard ICU procedure. Data were extracted from the ICU recording sheets for the time during which ICP and PbtO2 monitoring was in progress. With the addition of the ICMPlus® software recording system, measures of ICP, PbtO2, MAP and brain temperature were also be captured in samples averaged every 10 seconds.

Recordings of PaO2, PaCO2, haemoglobin (Hb) and saturation (SaO2) were obtained from arterial blood gas (ABG) samples taken routinely as per normal ICU protocols, and when clinically indicated. Serum sodium (Na) and Hb were documented from routine blood sample analysis.

Patient Management

Patient management was broadly based on current treatment guidelines for ICP and CPP in children [2, 5]. In general this involved treating ICP that was ≥ 20mmHg, and PbtO2 that was < 20mmHg. The cause of compromised PbtO2 was sought and treated when apparent; when this was not the case PbtO2 management followed an algorithmic approach. Further details of treatment are outlined in Appendix A.

Data Management

All data were managed in Microsoft Excel. Data cleaning was conducted as follows:

PbtO2 catheters were given a 2 hour settling period, and data during this time was excluded from analysis to avoid using potentially artefactual data from a stabilising catheter. Data from catheters that were incorrectly placed according to CT head scan (in grey matter rather than white matter) were not included, as was data from catheters placed in a pericontusional location. Where two catheters were inserted in the same patient, readings from the catheter located in normal-appearing 'uninjured' tissue were used, i.e. not in a pericontusional location.

To avoid skewed data analysis, recordings from patients who were terminal on admission were excluded, as was terminal data beyond the first hour of PbtO2 = 0. Observations recorded during various dynamic tests, such as autoregulation or FiO2 tests, were also excluded. Physiological data were manually reviewed in a step-wise process identifying artefacts, clear outliers, transcription errors and missing data points. Data from ABGs were used in correlation analysis with PbtO2 and ICP observations recorded at the same time that the ABG was taken.

Data Analysis

1. **Describing the profiles of ICP and PbtO2 following TBI**

Data used in this analysis included terminal data up to one hour of PbtO2 = 0 (single observation). Descriptive analysis on ICP and PbtO2 have been reported in terms of measures of central tendency; mean and median (where appropriate), and dispersion; range, inter-quartile range and standard deviation depending on the distribution of the observations. ICP and PbtO2 profiles were investigated as follows:

PbtO2

PbtO2 data for each patient were recorded as follows: lowest PbtO2 recorded during the monitoring period ($PbtO2_{low}$), median PbtO2 in the first 24 hours of monitoring ($mPbtO2_{24}$) or part thereof, and the number of episodes of PbtO2 < 5, PbtO2 < 10 and PbtO2 < 20 mmHg.

The PbtO2 profile was then investigated according to the following categories: the average, standard deviation and range of PbtO2 were calculated for the entire cohort. Using individual

patient data an overall $PbtO2_{low}$ and $mPbtO2_{24}$ were then calculated, as well as an average of the number of episodes of PbtO2 < 5, PbtO2 < 10 and PbtO2 < 20 mmHg. The temporal profile for each patient was investigated across the first seven days of monitoring post trauma, and the day of lowest PbtO2 was recorded.

ICP

ICP data for each patient was calculated as follows: the peak ICP recorded during the monitoring period (ICP_{peak}), median ICP in the first 24 hours of monitoring or part thereof (mICP24), and the number of episodes of ICP > 20 and ICP > 30 mmHg.

The ICP profile was then examined in a similar manner to PbtO2: the average, standard deviation and range of ICP were calculated for the entire cohort. Using individual patient data an overall ICP_{peak} and $mICP_{24}$ were then calculated, as well as an average of the number of episodes of ICP > 20 and ICP > 30 mmHg. The temporal profile for each patient was calculated across the first seven days of monitoring post trauma, and the day of highest ICP recorded. The number of patients being monitored for ICP and PbtO2 per day was also noted.

Trends in other physiological variables were analysed, and a summary of these is included for the purpose of providing descriptive information about the patient sample. These included: descriptive data for CPP, PaO2 (kPa), PaCO2 (kPa), Hb (g/dl) and Na (mmol/L) calculated for the entire cohort. Since this study focuses specifically on ICP and PbtO2, no further investigation for these variables was conducted.

2. Examining the time-linked relationship between ICP and PbtO2

Step 2.1: Evaluating the general relationship

Paired observations for ICP and PbtO2 were analysed with Spearman's correlation. Thereafter, a general estimating equation (GEE) model was constructed to control for the inter-individual variation in ICP and PbtO2 when assessing the relationship between the 2 variables. Additionally, simple logistic regression was performed to evaluate the relationship between ICP and PbtO2 dichotomised at 10 mmHg (PbtO2 < 10 mmHg and PbtO2 ≥10 mmHg).

Step 2.2: Controlling for potential confounding variables

To examine whether controlling for other variables improved the observed relationship between ICP and PbtO2, multiple linear regression was performed for ICP on PbtO2

(dependent variable), and a GEE model controlling for MAP, PaO2, PCO2, CPP and Hb were conducted. Spearman's correlation was also performed for PbtO2 and each of the controlled variables.

This step analysed only ICP and PbtO2 data recorded in conjunction with ABG data, but was conducted using 2 data sets. The first set contained data for all variables mentioned above. The second set was a restricted version of the first, in which data was limited to reasonable values of PaO2 (< 50 kPa), PaCO2 (3-6 kPa) and Hb (> 7 g/dl). This was to further adjust for the effect of any extreme values in these parameters that could potentially bias the analysis results.

3. Exploring critical threshold values of ICP and PbtO2

To explore critical threshold values of ICP and PbtO2 the sensitivities and specificities of ICP values for PbtO2 values were investigated to examine the predictive value of ICP for PbtO2. The sensitivity of a specific ICP value (ICP=Y) can thus be interpreted as the proportion of cases of PbtO2 below the designated threshold (low PbtO2) it was able to detect for ICP ≥ Y (a positive test), and the specificity of an ICP value represents the proportion of cases of low PbtO2 when ICP ≥ Y.

ICP and PbtO2 levels were investigated around critical values. PbtO2 (as the outcome variable) was dichotomised across three values: 1) PbtO2 < 5, and PbtO2 ≥ 5, 2) PbtO2 < 10, and PbtO2 ≥ 10, 3) PbtO2 < 20, and PbtO2 ≥ 20 mmHg. These categories were then each examined in relation to ICP collapsed into categories increasing in 5 mmHg increments. This allowed evaluation over narrow 'bands' of ICP: 1) ICP < 10, and ICP ≥ 10, 2) ICP < 15, and ICP ≥ 15, 3) ICP < 20, and ICP ≥ 20, 4) ICP < 25, and ICP ≥ 25, 5) ICP < 30, and ICP ≥ 30, 6) ICP < 35, and ICP ≥ 35, 7) ICP < 40, and ICP ≥ 40 mmHg. Sensitivities and specificities for each of these bands of ICP values were calculated for each of the 3 levels of PbtO2 as outcome. The relative risk for each level of ICP for low PbtO2 was also calculated.

Because there is a tradeoff between sensitivity and specificity for various threshold levels of ICP, to evaluate which threshold level would provide the best balance between sensitivity and specificity in detecting low brain oxygenation a receiver operating curve (ROC) was constructed. The ROC displays the efficacy of a range of tests (in this case ICP thresholds) by plotting sensitivity against 1-specificity with both axes ranging from 0 to 1.The diagonal of such a graph denotes that the test in question would accurately predict disease (in this case PbtO2 below the designated threshold) with no greater power than chance. The area under the curve equals the probability that a random sample with a positive result has a higher

value than a random sample with a negative result, and equals 0.5 under the diagonal (null hypothesis). In the context of this study an area of 0.8 for example would mean that a randomly selected patient with low brain oxygenation would have an ICP value greater than that for a randomly selected patient with adequate brain oxygenation 80% of the time. The ideal ROC would lie against the y-axis and the top of the graph would then continue parallel to the x-axis at a particular value below which the test would be very specific, and above which it would be very sensitive. However, since it is unlikely to see an ideal graph in reality, the efficacy of a test in detecting disease would be found by examining how far the curve lies away from the diagonal in the direction of the y-axis and is indicated by the area under the curve, where the perfect curve would have an area of 1.0 [147]. In this way the ROC provides a graphic presentation of the entire spectrum of sensitivity and specificity pairs for varying ICP thresholds across a spectrum of possible threshold values; in so doing the ROC is a useful test to monitor how alterations in the decision level of ICP thresholds can affect its sensitivity and specificity [26]. ROCs were constructed for ICP against PbtO2 < 5 mmHg, <10 mmHg, and < 20mmHg.

4. Age-related thresholds

To date little literature examining age-related ICP thresholds exists, and the most detailed categorization of age bands and ICP recommendations is provided by Chambers et al [26]. Based on age-related BP thresholds as well as the age at which the biggest incremental change in BP occurs the authors suggested the following age bands and provide recommended ICP threshold values for each: 2-6 years (ICP < 6.4 mmHg), 7-10 years (ICP < 8.7 mmHg) and 11-15 years (ICP < 13 mmHg).

Based on this work these age categories were adopted for this cohort for examination against PbtO2 to determine whether it improved the observed relationship between ICP and PbtO2: ICP threshold values were taken as 6 mmHg, 9 mmHg and 13 mmHg for each of the age groups respectively (rounded to the nearest whole number). Threshold values for each group were then designated the symbol 'X' (therefore X= 6, 9, 13 mmHg depending on the age category). PbtO2 was dichotomized for PbtO2 < 10 mmHg and PbtO2 ≥10 mmHg. This dichotomized data for each patient were then sorted for 1) ICP < X, and ICP ≥ X, 2) ICP <(X+5) and ICP ≥ (X+5), and 3) ICP < (X+10) and ICP ≥ (X+10) to examine the thresholds for ICP with age taken into account. Therefore, data was essentially interrogated in terms of 3 ICP levels: threshold, threshold + 5 mmHg and threshold + 10 mmHg. The sensitivities and specificities of these values of ICP were then investigated in the same manner as mentioned above. ROCs for each age group were plotted.

5. Evaluating the relationship between ICP and PbtO2 in individual patients

Using hourly and electronic data (where available) ROCs for individual patients were constructed. Where electronic data was used, median ICP and median PbtO2 were calculated over 1 hour periods for the duration of monitoring in each patient. Artefacts were identified and excluded. Median ICP was plotted against median PbtO2 in ROCs for PbtO2 < 10 and <20 mmHg and the diagnostic accuracy of ICP was indicated by the area under each curve.

6. Case Illustrations

Electronically recorded continuous data were interrogated to search for demonstrations of the dynamic relationship between ICP and PbtO2.

For examination of trends reflecting the relationship between ICP and PbtO2 exclusively, data points relating to external manipulation, such as suctioning, patient handling, increasing the FiO2, augmenting BP, autoregulation testing, as well as any clearly artefactual data points were excluded. Using the ICMPlus program a moving correlation coefficient between the means of ICP and PbtO2 was calculated over 2 minute intervals and plotted as a continuous trend. The means for ICP, PbtO2 and the correlation coefficient were calculated for the duration of the identified event.

When examining the role of pressure autoregulation MAP trends were also considered.

7. Data Capturing

To examine the relationship between manual and electronic recording of physiological data, the following was calculated: 1) hourly data were compared with electronic data averaged over the half hour preceding and following the corresponding hour (mean-hour), 2) the number of episodes of ICP > 20 mmHg and PbtO2 < 20 mmHg lasting 5 minutes or longer were compared with the number of episodes recorded across hourly data. Analysis was conducted with the first 24 hours of complete data available.

In keeping with the recommendations of Bland and Altman [12] the degree of agreement between electronic and hourly recorded data for mean-hour was calculated as outlined: Mean ICP and mean PbtO2 were calculated using electronic and hourly ICP and PbtO2 readings. The mean difference between electronic and hourly ICP data was then calculated and plotted against mean ICP, and the mean difference between electronic and hourly PbtO2 data was calculated and plotted against mean PbtO2. In order to summarise the degree of agreement between these two measurement techniques, for each of the graphs two lines of agreement were plotted at the level of 2 standard deviations above and below the mean difference value.

These lines indicate the extent to which values vary about the mean difference and therefore the extent to which electronic and hourly data differ from each other. Variation within two standard deviations suggests adequate agreement between the two recording measures. Provided that differences within two standard deviations would not be of clinical importance these techniques could then be used interchangeably. The number of episodes of high ICP or low PbtO2 was compared using the proportions z test.

Chapter 8

RESULTS

Data for 81 patients who underwent ICP and PbtO2 monitoring for severe TBI from June 2006 to June 2009 were collected. Data from 5 patients were excluded due to incorrect or penumbral placement of the catheter (n=3) or because the patient was terminal on admission (n=2). Terminal data excluded from the 75 remaining patients accounted for 7% of the total number of observations, dynamic tests such as autoregulation and FiO2 tests accounted for 0.3% and missing data points accounted for 8.7%. Exclusion of data was distributed across the cohort.

Admission Clinical and Demographic Data

Demographic and admission clinical data are summarised in Table 1. The age distribution of this cohort was as follows: < 2 years (n=11, 14.7%), 2-6 years (n=32, 42.7%), 7-10 years (n=20, 26.7%), and 11-15 years (n=12, 16%).

Time sequence

The median number of hours to monitoring post injury was 7 (IQR 7-17 hours). Monitoring was started ≤ 12 hours after injury in 44 patients (66.7 %), between 13 and 24 hours in 16 patients (24.2%) and > 24 hours in 6 patients (9%). The average duration of monitoring was 5.8 ± 3.2 days (range 1-15 days), and on average patients stayed in ICU for 7.9 ± 4.2 days (range 1-21 days).

Physiological Data

Physiological data for the patient cohort are summarised in Table 2. Technical problems were encountered with 2 ICP catheters which required replacement. No technical problems arose with PbtO2 catheters, although both PbtO2 and ICP catheters had to be replaced in one patient in whom they were inadvertently pulled out. CT scans were checked to ensure that catheter placement was correct in all patients. Data were excluded from analysis from patients where the catheter had been misplaced in grey matter on follow-up head CT scans (n= 2). There were no complications associated with the ICP or PbtO2 catheters.

Table 1

Admission clinical and demographic characteristics (N= 75)

Characteristic		**Value**
Age		6.4 ± 3.5 years (4 months – 14 years)
Gender	Male	49
	Female	26
Post resuscitation GCS		3
	GCS 3	3
	GCS 4	12
	GCS 5	14
	GCS 6	18
	GCS 7	14
	GCS 8	11
Motor component of GCS (median, range)		4 (1- 5)
Pupil reaction on admission		
	Bilaterally reactive	57 (76%)
	Unilaterally nonreactive	4 (5.3%)
	Bilaterally nonreactive	10 (13.3%)
Initial Hb		9.9 ± 1.7
Mechanism of Injury		
	MVA passenger	17 (22.6 %)
	MVA pedestrian	43 (57.3 %)
	Crush injury	3 (4 %)
	Gunshot to head	4 (5.3 %)
	Fall from height	1 (1.3 %)
	Stab to head	2 (2.6 %)
	NAI	2 (2.6 %)
	Blunt head injury/assault	2 (2.6 %)
	Other	1 (1.3 %)
Polytrauma		46 (61.3 %)

Note: Values are expressed as mean ± SD (or median and range were specified) or as numbers and proportions. Patients who did not have a postresuscitation GCS ≤ 8 deteriorated to this level after admission. Polytrauma was defined as all injuries to organ systems other than the head, excluding superficial wounds. MVA: Motor vehicle accident, NAI: non-accidental injury.

Table 2

Summary of physiologic monitored variables for total monitored time

Variable	Value
PbtO2 (mmHg)	32.6 ± 12.7 Range (0-98.9)
MAP (mmHg)	81.8 ± 13.1
ICP (mmHg)	14.5 ±7.7 Range (0-100)
CPP (mmHg)	67.16 ± 15.09
PaO2 (kPa)	17 (12.2-25) Range (4.2-78.1)
PaCO2 (kPa)	4.6 ± 1.1
SaO2 (%)	99 (98-100) Range (30-100)
FiO2 (%)	40 (40-60) Range (10-100)
Haemoglobin (g/dl)	10.8 ± 1.8
Serum sodium (mmol/L)	143 ± 4.0

Note: Values reported as mean ± SD, or median, IQR and range depending on distribution characteristics of observations. Descriptive data calculated on 9452 observations, terminal data beyond first hour PbtO2 = 0 excluded

Analyses

1. **Describing the profiles of ICP and PbtO2 following TBI**

Data used to examine the profiles of ICP and PbtO2 totalled 9452 hourly observations. Profiles for ICP and PbtO2 are summarised in Table 3.

Values for mPbtO2, $mPbtO2_{24}$ and median $PbtO2_{low}$ were 32.6 mmHg, 29.7 mmHg and 12.1 mmHg respectively. Despite treatment aimed at maintaining PbtO2 > 20 mmHg, 66 patients experienced episodes of PbtO2 < 20 mmHg (88%), 35 patients experienced PbtO2 <10 mmHg (46.7%), and 14 had episodes of PbtO2 < 5 mmHg (18.7%). The mICP for the monitoring period was 14.5 mmHg and the median for the first 24 hours of monitoring was 13.76 mmHg. ICP peaked at an average of 33.6 mmHg; 63 (84%) patients experienced episodes of ICP > 20 mmHg, and 40 (53.3%) patients ICP > 30 mmHg.

Table 3

PbtO2 and ICP Profiles

PbtO2 (mmHg)		
	PbtO2 low	Mdn 12.1 (7.3-16.8) Range (0.5-29.1)
	PbtO2 24	Mdn 29.71 (23.7-34.98) Range (2.1-56)
	PbtO2 < 5 (no. of episodes)	Ave 4.92 Range (1-16)
	Number of patients	14 (18.7%)
	PbtO2 <10 (no. of episodes)	Ave 4.74 Range (1 -22)
	Number of patients	35 (46.7%)
	PbtO2 < 20 (no. of episodes)	Ave 17.3 Range (1-122)
	Number of patients	66 (88%)
ICP (mmHg)		
	ICP peak	Mdn 30 (22-41) Range (9-99)
	ICP24	Mdn 13.76 (10.83-18.17) Range (2.6-60.7)
	ICP > 20 (no. of episodes)	Ave 27.2 Range (1-142)
	Number of patients	63 (84%)
	ICP > 30 (no. of episodes)	Ave 7.4 Range (1-48)
	Number of patients	40 (53.3%)

Note: Calculated from individual patient values. Values reported as median, IQR and range, or average and range where specified.

The temporal outline of ICP and PbtO2 trends for the first week of monitoring are graphically displayed in Figures 1 and 2. Mean PbtO2 over the first week was 32.4 ± 3.8 mmHg. The mPbtO2 increased from day 1 to day 6, after which it began to decrease. The difference between days was most marked between days 1 and 2 which exhibited a 5.7 mmHg increase on average. The day of lowest mPbtO2 was day 1 (24.5 mmHg) and the day of highest mPbtO2 was day 6 (34.9 mmHg).

Mean ICP during the first week of recording was 14.2 ± 2.18 mmHg. There was little change in mean values for ICP over the whole of the first week. Mean ICP declined slightly from day 1 to day 5, after which it rose again slightly over days 6 and 7. The greatest change in ICP occurred between days 1 and 2 in which time ICP decreased by 1.2 mmHg. The day of highest mICP was day 1 (15.9 mmHg) and mICP was lowest on day 5 (13.8 mmHg).

Figure 1

PbtO2 Profile for the first week of monitoring

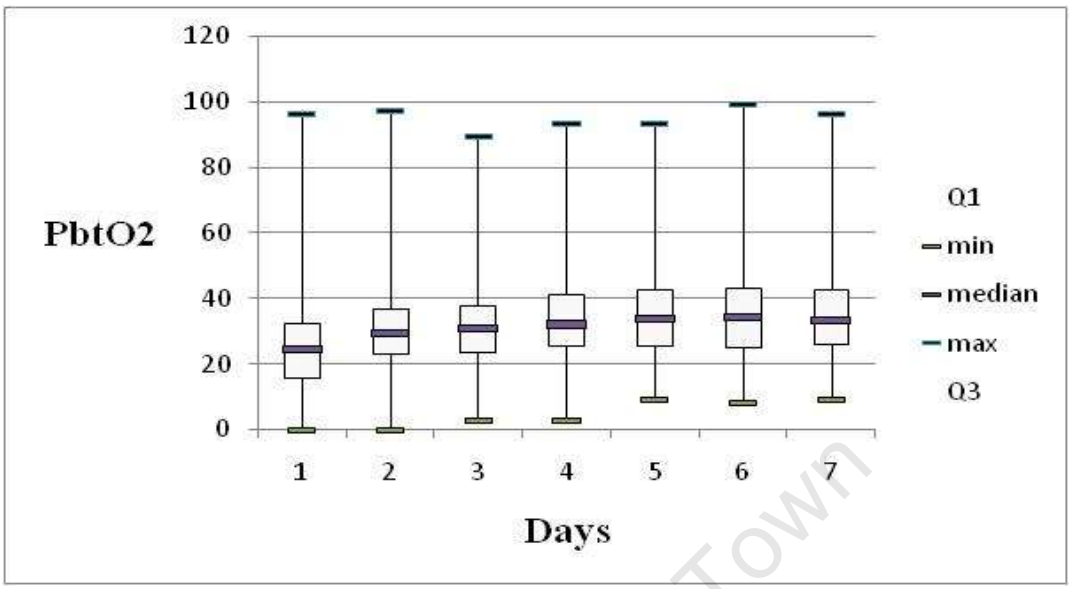
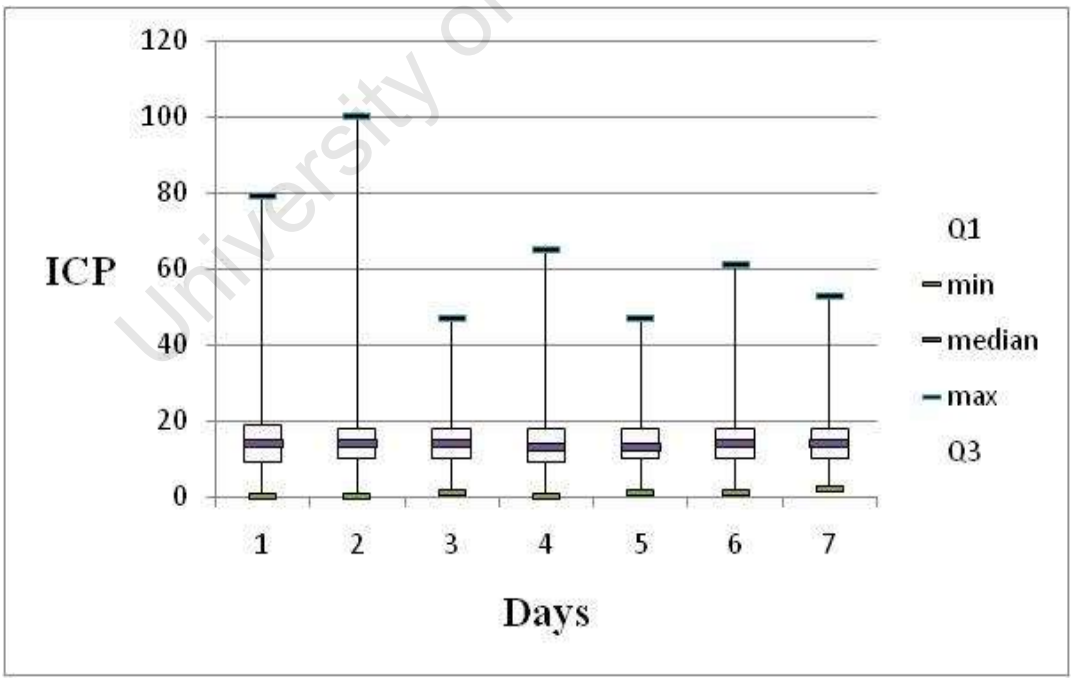


Figure 2

ICP Profile for the first week of monitoring



The number of patients who had monitored data increased from day 1 to day 2 post-injury (Table 4), largely due to the later insertion of catheters in many patients. Fewer patients were monitored as the week progressed, reflecting patient recovery and discontinuation of monitoring. By the third day 60% of patients had experienced their highest ICP value, but ICP continued to peak in some patients until after day 7. Lowest PbtO2 values were recorded in more than 70% of patients by day 3, but low values continued to occur beyond day 7.

Table 4

ICP and PbtO2 during the first week of monitoring

Day	No. Patients being monitored	Patients with highest mICP	Cumulative %	Patients with lowest mPbtO2	Cumulative %
1	56	14	18.67	25	33.33
2	69	15	38.67	19	58.67
3	69	17	61.33	11	73.33
4	61	8	72	4	78.67
5	53	6	80	3	82.67
6	43	6	88	7	92
7	34	6	96	2	94.67

Note: Column 3 and 5 reflect the number of patients who experienced their highest ICP or lowest PbtO2 on that respective day. These are expressed as percentages of the cohort of 75 patients in the 4th and 6th column.

2. Examining the time-linked relationship between ICP and PbtO2

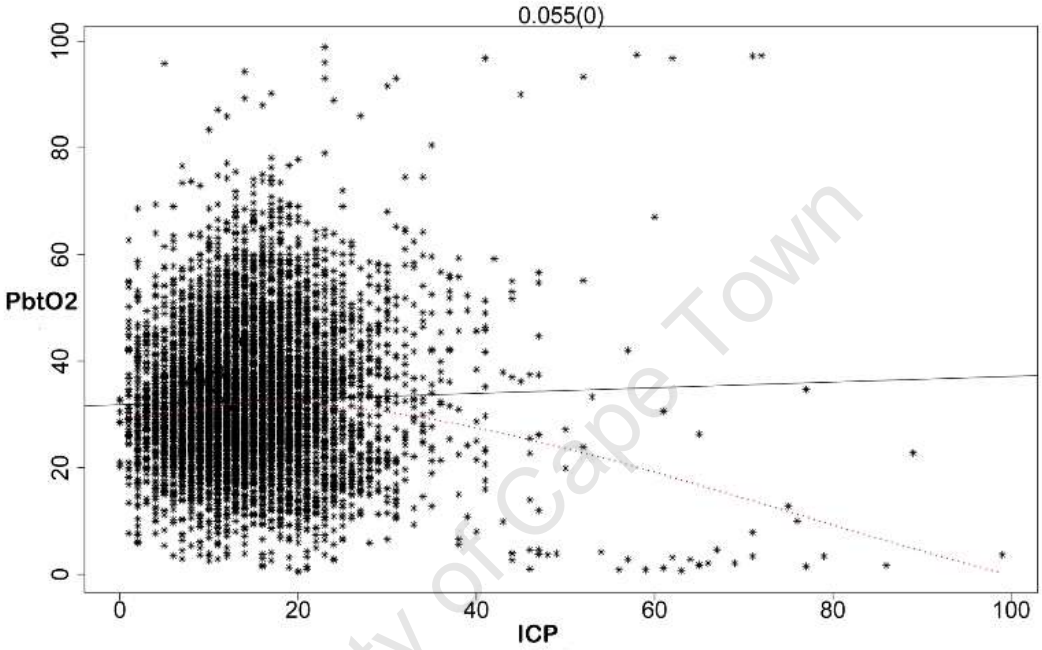
Step 2.1: Evaluating the relationship in general

Analyses for paired ICP and PbtO2 observations were performed on data which excluded all terminal and missing data points. Spearman's correlation using 8389 observations revealed a positive weak correlation between ICP and PbtO2 ($r = 0.05$, $p < 0.01$). The scatter plot is provided in Figure 3. The GEE model indicated that controlling for inter-individual variation also did not reveal a significant relationship between ICP and PbtO2 ($p = 0.86$), but that intra-individual PbtO2 values were influenced by individual characteristics *(intraclass coefficient = 0.33, $p < 0.01$)*. Logistic regression showed that higher values of ICP were associated with a lower probability of PbtO2 ≥10 mmHg, however this relationship was once

again weak (*estimate = -0.075, p < 0.01*). The odds ratio was 0.93, with a confidence interval of 0.92 – 0.94.

Figure 3

Scatter plot: Correlation between ICP and PbtO2



Step 2.2: Controlling for potential confounding variables

Linear regression analysis for ICP and PbtO2 controlling for MAP, CPP, PaO2, PaCO2 and Hb was performed. Results from neither the unrestricted (400 observations) nor the restricted data set (334 observations) revealed a significant relationship between PbtO2 and ICP (*r = -0.107, p =0.27*) and (*r= -0.104, p =0.32*). Therefore, controlling for these additional variables did not improve the observed relationship between ICP and PbtO2; however, much fewer data points were used than in the pooled analysis of all observations for ICP and PbtO2. Only MAP, CPP and PaO2 showed a significant although weak positive relationship with PbtO2. Results from the GEE models differed across the 2 data sets in terms of PaCO2; the unrestricted data set indicated that PaCO2 had a significant positive relationship with PbtO2 once intra-individual variation had been controlled for *(estimate=1.64, p<0.01),*

whereas the restricted data set did not exhibit this relationship. Correlations between PbtO2 and ICP, MAP, CPP, PaO2, PaCO2 and Hb are shown in Table 5.

Table 5

Table of Correlations with PbtO2: Linear Regression

Variable	Correlation Value (r)	
	Unrestricted Data	Restricted Data
ICP	-0.07	-.05
MAP	0.22*	0.18*
CPP	0.22*	0.19*
PaO2	0.18*	0.14*
PaCO2	-0.1	-0.15
Hb	-0.07	-0.04

Note: * Denotes significant correlations ($p < 0.01$).

3. Exploring critical threshold values of ICP and PbtO2

A total of 8389 data points for ICP and PbtO2 less terminal data were used for this analysis. Frequencies for data dichotomized for PbtO2 of 5, 10 and 20 mmHg and for ICP dichotomized across 5, 10, 15, 20, 25, 30, 35, and 40 mmHg are summarised in Table 6. The sensitivities and specificities for each of these data sets are shown in Table 7.

3.1 Sensitivity and specificity

An ICP threshold of 20 mmHg (ICP ≥ 20) detected 64% of episodes of PbtO2 < 5 mmHg (i.e. 64% of the total number of these episodes occurred when ICP was ≥ 20), 42% of PbtO2 < 10 mmHg, and 29% of PbtO2 < 20 mmHg. The specificity for ICP of 20 mmHg was approximately 81% for all categories of PbtO2 thresholds. An ICP of 15 mmHg detected 79% of PbtO2 < 5 mmHg, 61% of PbtO2 < 10 mmHg, and 51% of PbtO2 < 20. This level of ICP demonstrated a specificity of approximately 55% in all cases of PbtO2. These results indicate that an ICP threshold of 15 mmHg detects more cases of lower brain oxygenation than a threshold of 20 mmHg for the same threshold values of PbtO2, but that only about half of the cases detected do in fact have low brain oxygenation. ICP thresholds of 20, 15 and 10 mmHg all detected proportionally fewer cases of low brain oxygenation as the

threshold value of PbtO2 increased. As PbtO2 decreased, higher ICP values picked up proportionally more numbers of low PbtO2, suggesting that the lower the PbtO2, the more likely it is associated with high ICP. As ICP thresholds increased sensitivity for low brain oxygenation decreased (more episodes of low PbtO2 were detected at lower ICP thresholds), but specificity increased. The fact that all ICP thresholds exhibited similar specificity levels for each category of PbtO2 may be explained by the fact that the overwhelming number of observations always fell into the disease negative (PbtO2 greater than threshold) and test negative (ICP lower than threshold) categories, with which specificity is calculated. Therefore the proportions between disease negative and test negative frequencies were relatively similar for all ICP thresholds and all PbtO2 categories.

Table 6

Frequency table for dichotomised ICP and PbtO2 data

		PbtO2					
		PbtO2 < 5	**PbtO2≥ 5**	**PbtO2< 10**	**PbtO2≥ 10**	**PbtO2 <20**	**PbtO2≥ 20**
	Total	56	8333	154	8235	1113	7276
ICP	**ICP < 10**	4	1990	27	1966	240	1753
	ICP ≥ 10	52	6343	127	6269	873	5523
	ICP < 15	12	4627	60	4579	544	4095
	ICP ≥ 15	44	3706	94	3656	569	3181
	ICP < 20	20	6765	89	6696	786	5999
	ICP ≥ 20	36	1568	65	1539	327	1277
	ICP < 25	29	608	116	7638	956	6798
	ICP ≥ 25	27	7725	38	597	157	478
	ICP < 30			120	8003	1044	7079
	ICP ≥ 30			34	232	69	197
	ICP < 35					1070	7189
	ICP ≥ 35					43	87
	ICP < 40			124	8180	1076	7228
	ICP ≥ 40			30	55	37	48

Note: The number of ICP levels calculated for each value of PbtO2 was dependent on the availability of sufficient data in that category.

Table 7

Sensitivities and Specificities calculated for dichotomised data

		PbtO2 = 5	
		Sensitivity	**Specificity**
ICP	**ICP = 10**	92.85 (82-98)	23.88 (22-24)
	ICP = 15	78.57 (65-88)	55.52 (54-56)
	ICP = 20	64.28 (50-76)	81.18 (80-82)
	ICP = 25	48.21 (34-61)	92.7 (92-93)
		PbtO2 = 10	
		Sensitivity	**Specificity**
ICP	**ICP = 10**	82.46 (75-88)	23.87 (22-24)
	ICP = 15	61.03 (52-68)	55.6 (54-56)
	ICP = 20	42.2 (34-50)	81.31 (80-82)
	ICP = 25	24.67 (18-32)	92.75 (92-93)
	ICP = 30	22.07 (15-29)	97.18 (96-97)
	ICP = 40	19.48 (13-26)	99.33 (99-99)
		PbtO2 = 20	
		Sensitivity	**Specificity**
ICP	**ICP = 10**	78.43 (75-80)	24.09 (23-25)
	ICP = 15	51.12 (48-54)	56.28 (55-57)
	ICP = 20	29.38 (26-32)	82.44 (81-83)
	ICP = 25	14.1 (12-16)	93.43 (92-93)
	ICP = 30	6.19 (4-7)	97.29 (96-97)
	ICP = 35	3.86 (2-5)	98.8 (98-99)
	ICP = 40	3.32 (2-4)	99.34 (99-99)

Note: values are reported with 95% confidence interval

3.2 Relative risk

The relative risk for each level of ICP per category of PbtO2 is presented in Table 8 and the change per ICP threshold is plotted in Figures 4-6. The likelihood of PbtO2 < 5, 10 and 20 mmHg occurring increased as the value of ICP increased. The largest increase in relative risk per threshold value of ICP was seen for PbtO2 = 5 mmHg, for which the median change was 3.08 % (0.48 – 3.75 %). However, the most marked increase in relative risk was between ICP = 30 mmHg and ICP = 40 mmHg for PbtO2 < 10 mmHg (14.98%). The likelihood of PbtO2 < 10 was 1.15% greater for an ICP threshold of 20 mmHg than for ICP of 15 mmHg, and the likelihood of PbtO2 < 20 was only 0.46 % greater for ICP of 20 mmHg in comparison to ICP of 15 mmHg.

Table 8

Relative Risk: PbtO2 = 5

ICP	Relative Risk
ICP = 10	4.05 (1.41-13.16)
ICP = 15	4.53 (2.32-9.05)
ICP = 20	7.61 (4.29-13.6)
ICP = 25	11.37 (6.57-19.66)

Relative Risk: PbtO2 = 10

ICP	Relative Risk
ICP = 10	1.46 (0.96-2.27)
ICP = 15	1.94 (1.39-2.7)
ICP = 20	3.09 (2.25-4.28)
ICP = 25	4.0 (2.75-5.8)
ICP = 30	8.65 (5.9-12.53)
ICP = 40	23.64 (16.31-32.86)

Relative Risk: PbtO2 = 20

ICP	Relative Risk
ICP = 10	1.13 (0.99-1.3)
ICP = 15	1.29 (1.16-1.45)
ICP = 20	1.76 (1.56-1.98)
ICP = 25	2.0 (1.72-2.33)
ICP = 30	2.02 (1.61-2.49)
ICP =35	2.55 (1.94-3.26)
ICP = 40	3.36 (2.53-4.25)

Note: Values are rounded to the nearest decimal place. Values reported with 95% confidence interval.

Charts of Changes in Relative Risk for ICP

Figure 4: PbtO2 = 5 mmHg

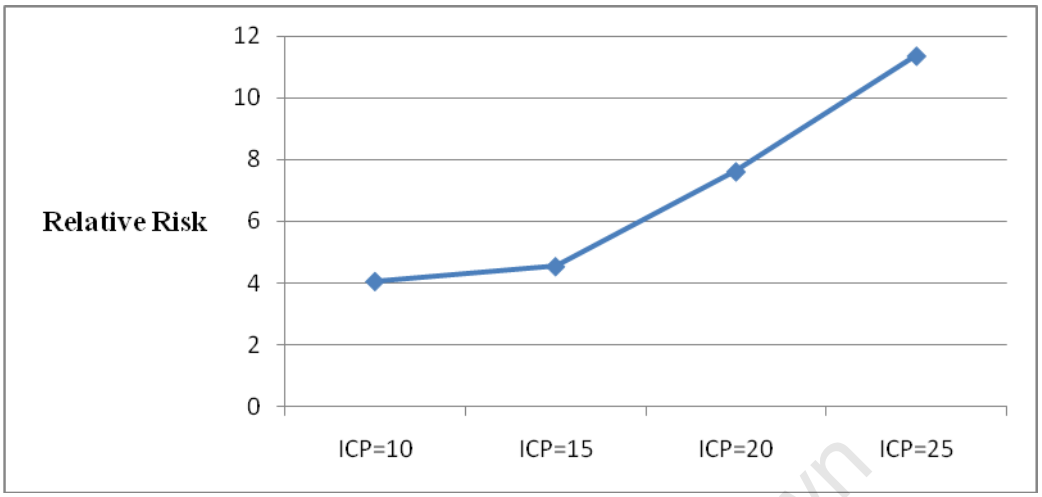


Figure 5: PbtO2 = 10 mmHg

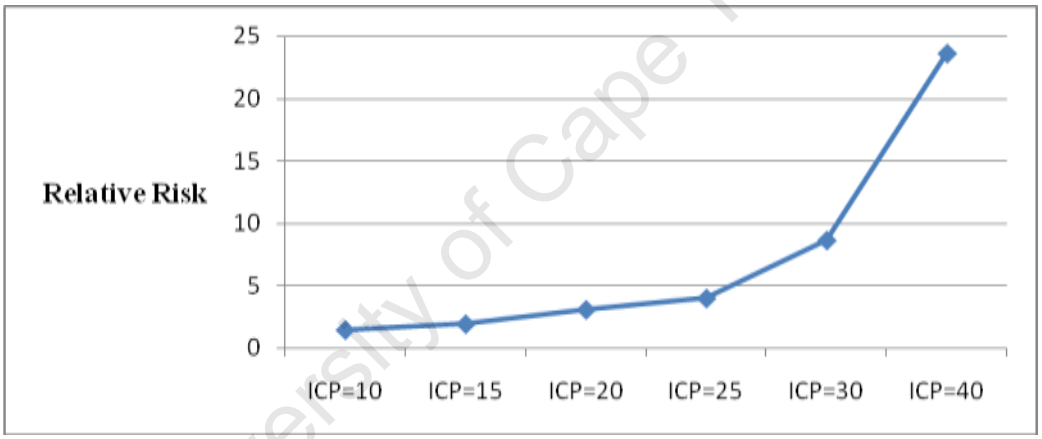
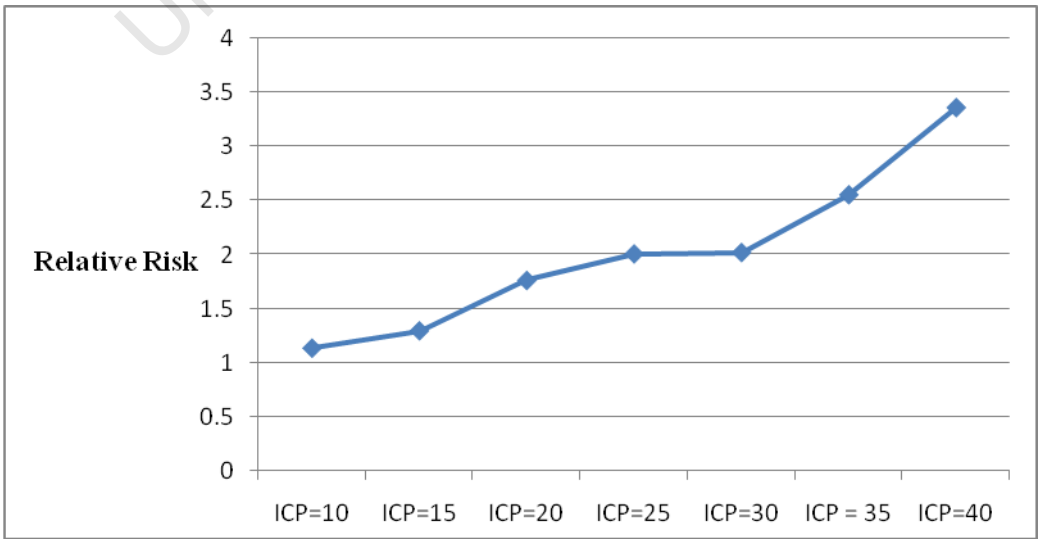


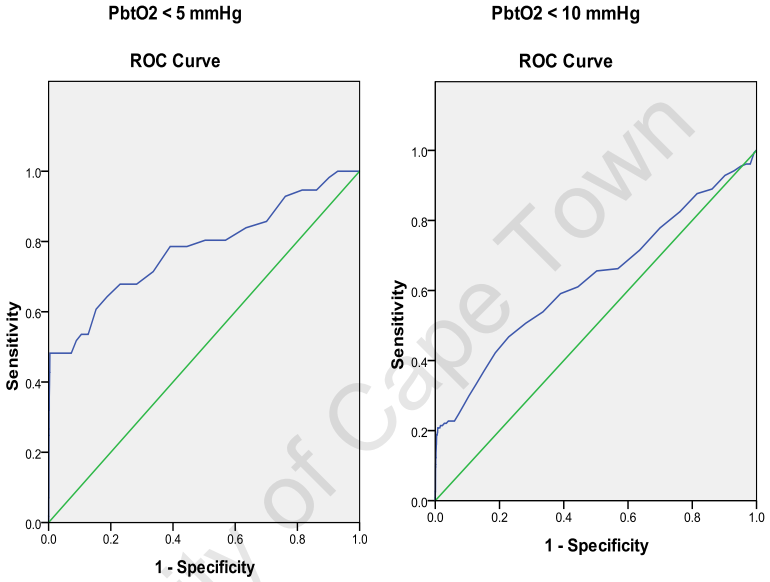
Figure 6: PbtO2 = 20 mmHg

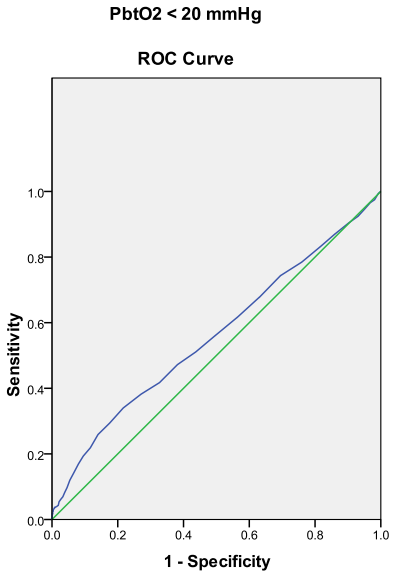


3.3 ROCs

The ROCs for ICP in general were poor, and the curves mostly lay close to the diagonal line. The area under the curve was 0.778 for PbtO2 < 5 mmHg, 0.631 for PbtO2 < 10 mmHg, and 0.559 for PbtO2 < 20 mmHg. The ICP threshold value with the best combination of sensitivity and specificity was approximately 15.5 mmHg for PbtO2 < 5 and < 10 mmHg, and 19.5 mmHg for PbtO2 < 20 mmHg. The three ROCs are depicted in Figures 7-9.

Figures 7-9: Receiver Operating Curves for Pooled Data





4. Age-related thresholds

Frequencies for data dichotomized for PbtO2 = 10 mmHg and for ICP of X, (X+5) and (X+10) are outlined in Table 10. ICP = X [6, 9, 13 mmHg] detected just over 90% of cases of PbtO2 < 10 mmHg but only had a specificity of about 19%. ICP = (X+5) [11, 14, 18 mmHg] had a sensitivity of 63.3 % for PbtO2 < 10 mmHg and a specificity of 46.3%. ICP=(X+10) [16, 19, 23 mmHg] detected approximately 46% of cases with a specificity of almost 75%.

Table 9

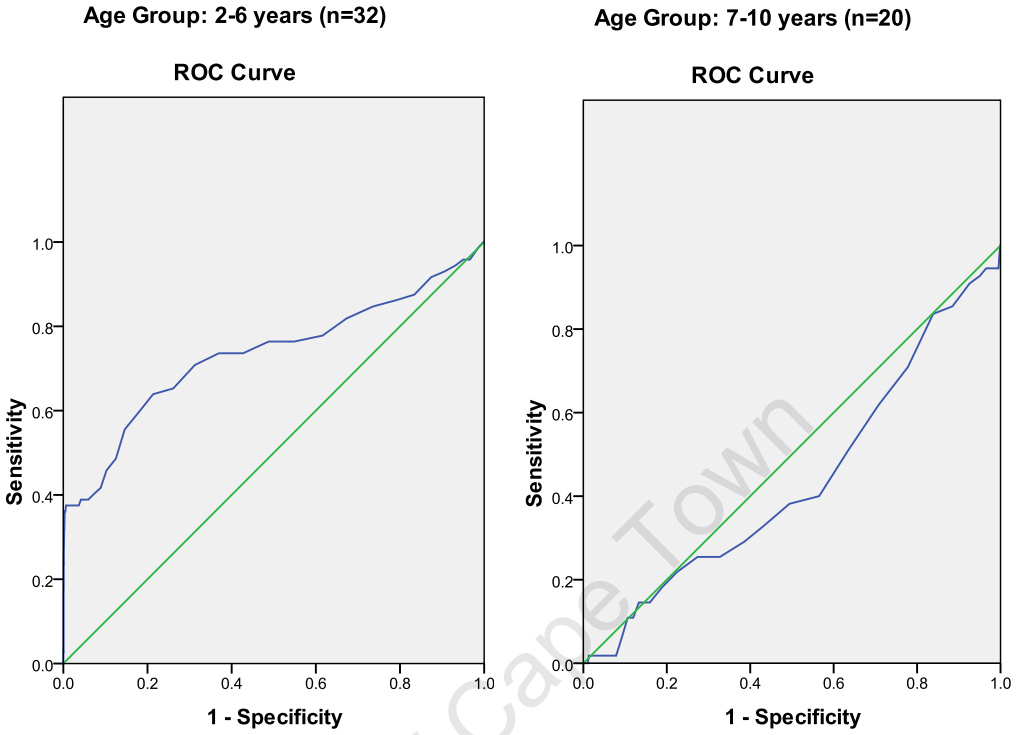
Frequency table for age-related ICP thresholds

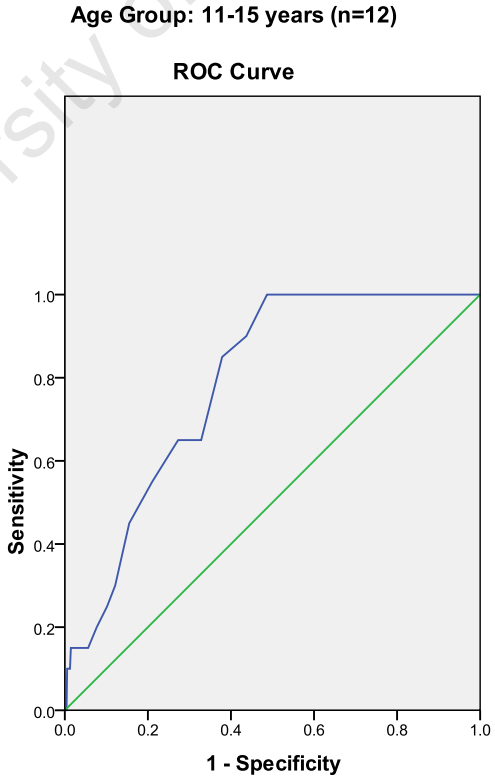
	PbtO2 < 10	**PbtO2 ≥ 10**
Total	147	6648
ICP < X	14	1246
ICP ≥ X	133	5402
ICP < (X+5)	54	3076
ICP ≥ (X+5)	93	3572
ICP < (X+10)	86	4978
ICP ≥ (X+10)	67	1670

The age-related ROCs (Figures 10-12) were no stronger than those plotted for the entire sample and the curve for age group 7-10 years even fell below the diagonal. The area under the curve was 0.733 for 2-6 years, 0.438 for 7-10 years, and 0.785 for 11-15 years. The fact that the 7-10 year ROC fell below the diagonal may be explained firstly by the weak relationship between ICP and PbtO2 in general, and secondly, by the fact that low values of PbtO2 in 2 of the patients in this age group were attributed to other causes; one patient had probable fat embolism syndrome, and the second patient suffered from multiple organ dysfunction syndrome (MODS). However, although the area under the ROC improved somewhat after these 2 patients were excluded, the curve still remained below the diagonal. It is also possible that the thresholds selected for the age groups, or even the range of ages selected for these groups, are not optimal. However, there is no better data for age-related thresholds in children currently.

Figures 10-12

Age-related ROCs for PbtO2 < 10 mmHg



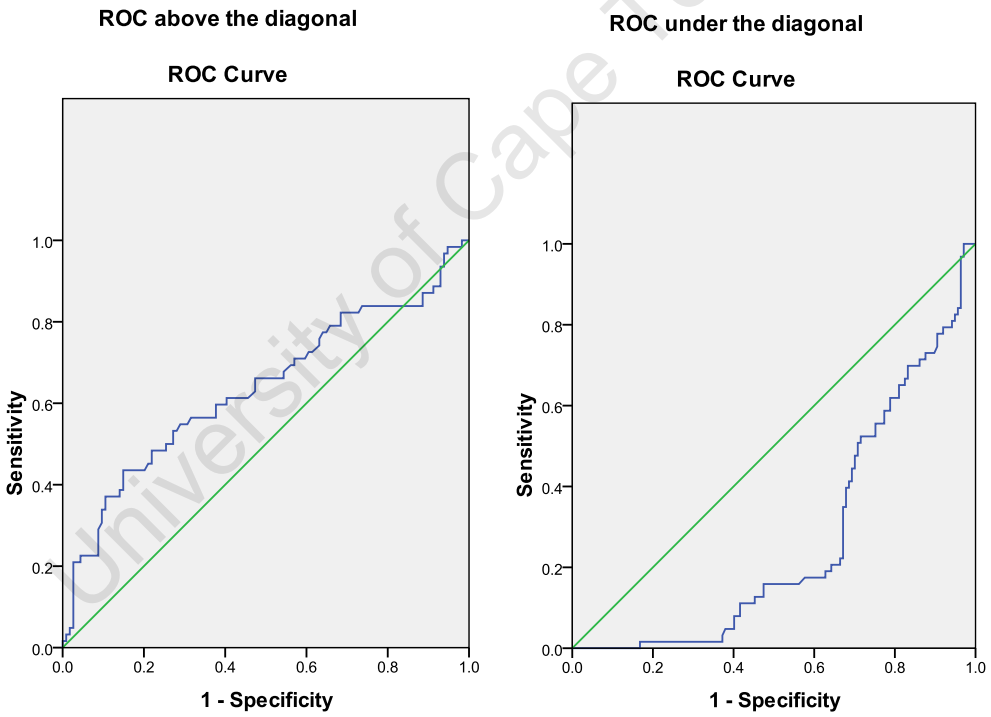


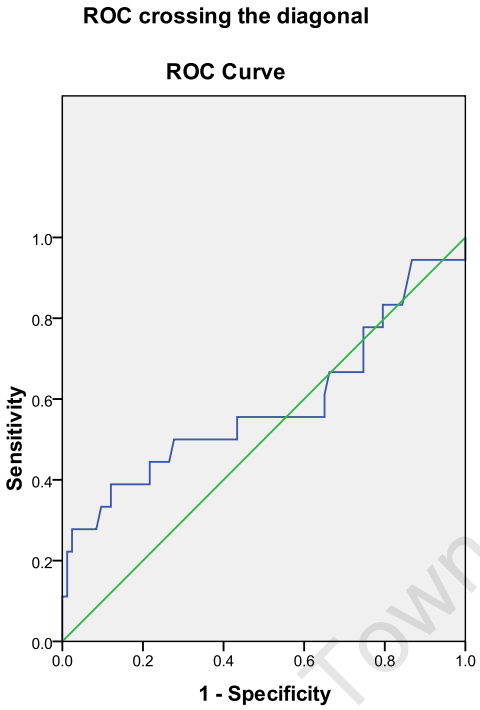
5. Evaluating the relationship between ICP and PbtO2 in individual patients

ROCs for individual patients showed significant variation but in general were not better than ROCs for pooled data. ROCs for 3 patients are selected here (Figure 13-15) to illustrate the differences in curves obtained; one patient had an ROC which lay above the diagonal (area = 0.64), another had an ROC which fell below the diagonal (area = 0.28), and the third patient's ROC crossed the diagonal (area = 0.58). These findings suggest that the relationship between ICP and PbtO2 demonstrates heterogeneity among individual patients, and that the association between ICP and compromised PbtO2 may vary between individuals, which influences the general relationship observed in ROCs for pooled data.

Figures 13 – 15

ROCs for individual patients





6. Case Illustrations

Interrogation of electronic data revealed a number of different patterns between ICP and PbtO2.

Linear negative relationship: Figure 16 and 17 depict a linear negative relationship between ICP and PbtO2 in the context of stable MAP and systemic oxygenation. The mean correlation coefficients between ICP and PbtO2 for the spike in Figures 16 and 17 were -0.72 and -0.55 respectively, suggesting that ICP had a strong negative influence on PbtO2. The lower coefficient for Figure 17 may be explained by the fact that there is a slight delay in the drop in PbtO2 following the ICP rise, and also by the fact that ICP spikes initially precipitously and then drops to a slightly lower level; this event could result in a transient positive correlation which would lessen the average correlation coefficient. Figure 18 depicts a 5-hour period in which several examples of the negative linear change in ICP and PbtO2 can be seen.

Figure 16

Illustrations of the negative linear relationship between ICP and PbtO2

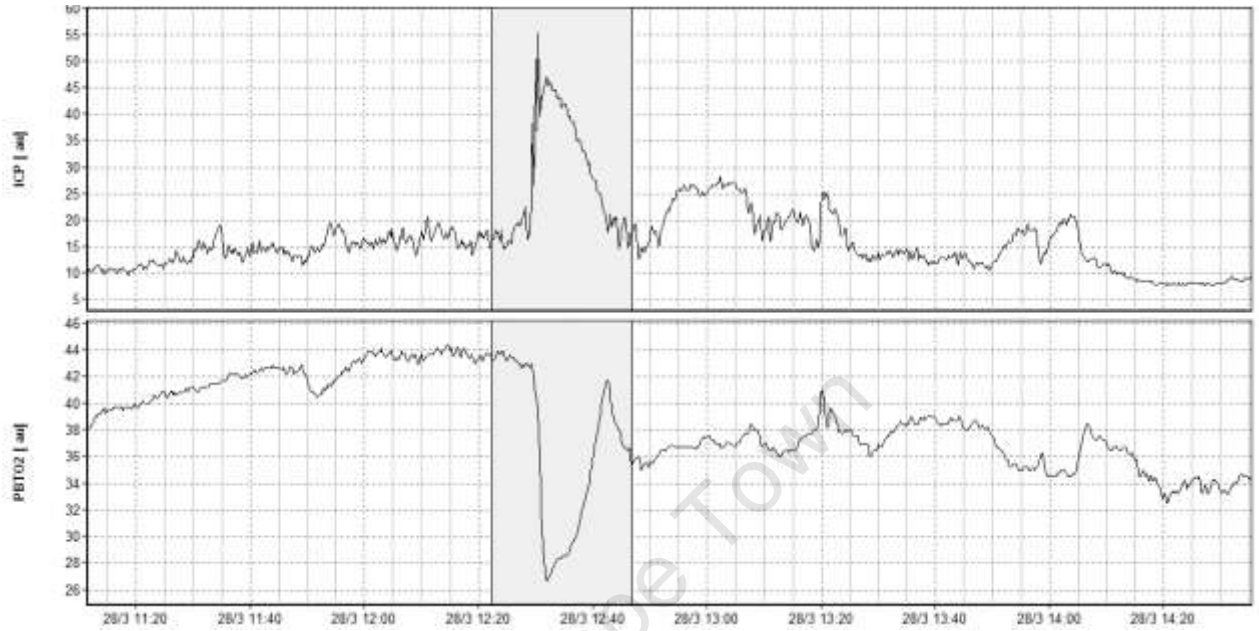


Figure 17

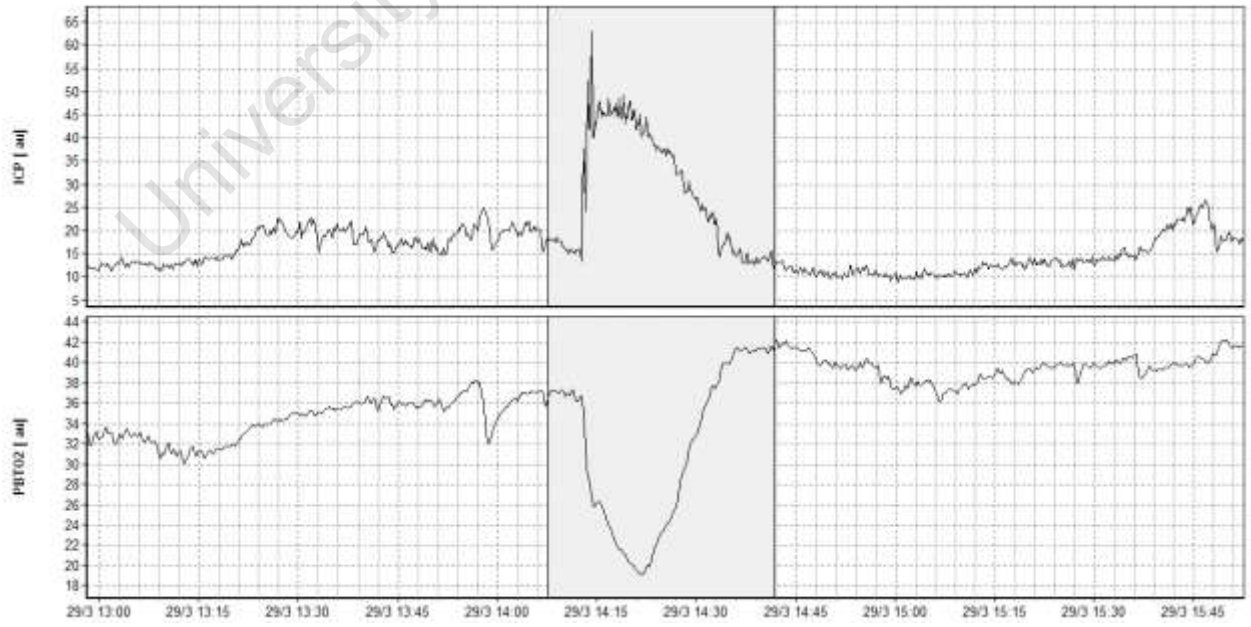
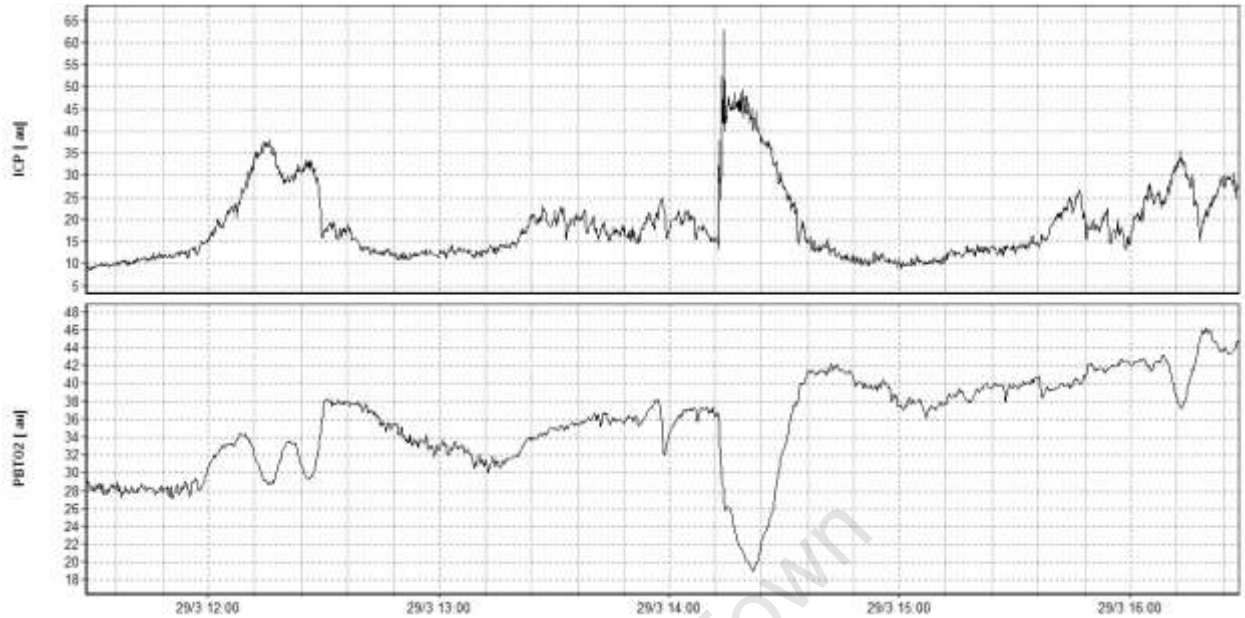
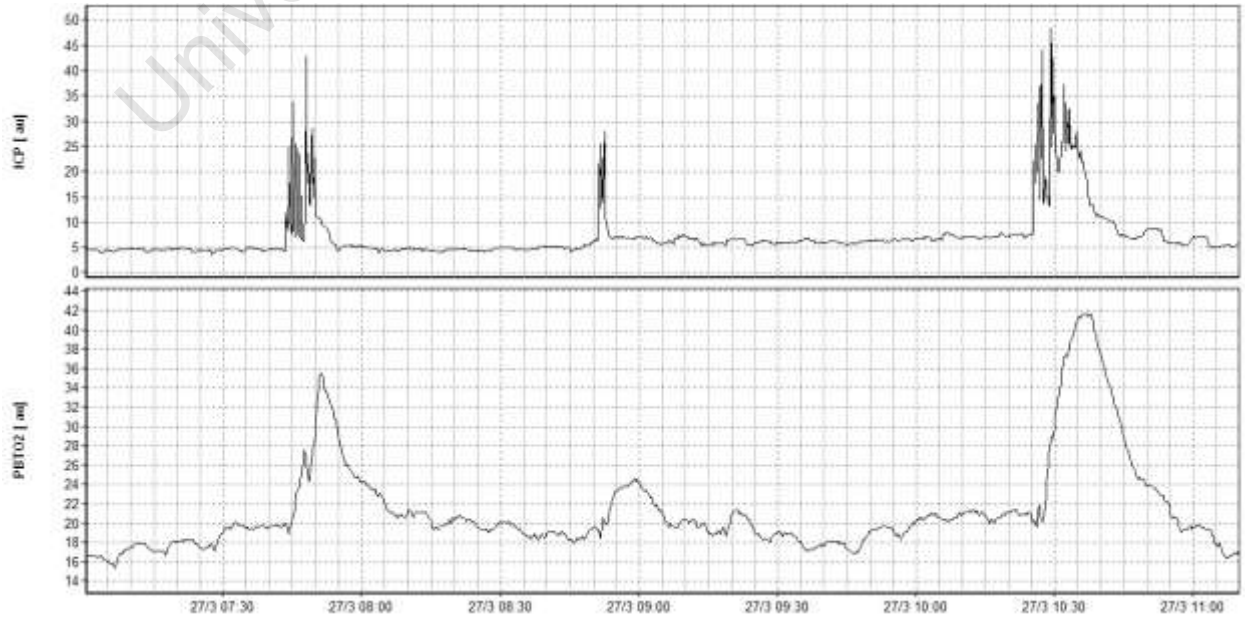


Figure 18



Linear positive relationship: Figure 19 highlights a period of approximately 4.5 hours across which a number of examples of a positive relationship between ICP and PbtO2 are observed (not related to external handling). The correlation coefficients for the ICP spikes are low, with the highest coefficient being 0.22 for the ICP spike occurring at 10:30. Reasons for this may be once again the delay in the take-off in PbtO2, and also the fluctuating nature of the ICP peak, but the temporal relationship between the 2 variables is clear. MAP throughout this period was stable.

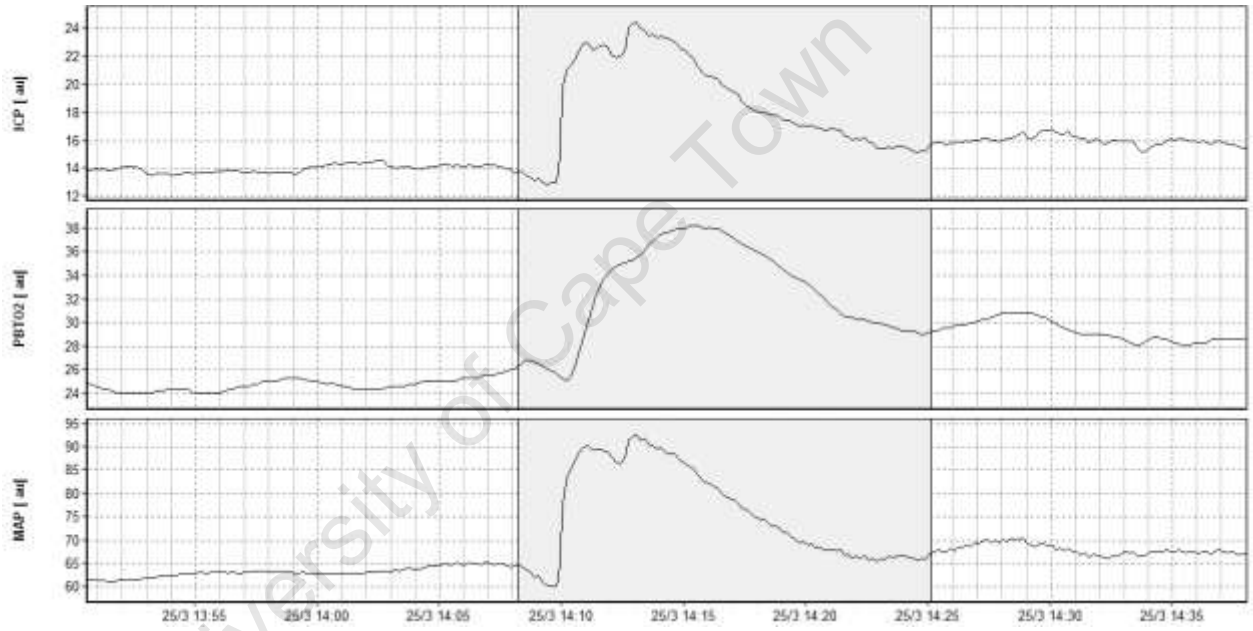
Figure 19: Illustration of the positive linear relationship between ICP and PbtO2



Changes in ICP and PbtO2 as a function of pressure autoregulation: Figure 20 illustrates how impaired pressure autoregulation (confirmed with transcranial Doppler) can result in a simultaneous increase in ICP and PbtO2 during an increase of MAP. The increase in MAP is accompanied by an instantaneous rise in ICP and a slightly delayed increase in PbtO2. These changes are indicative of a passive vascular response to increased blood pressure.

Figure 20

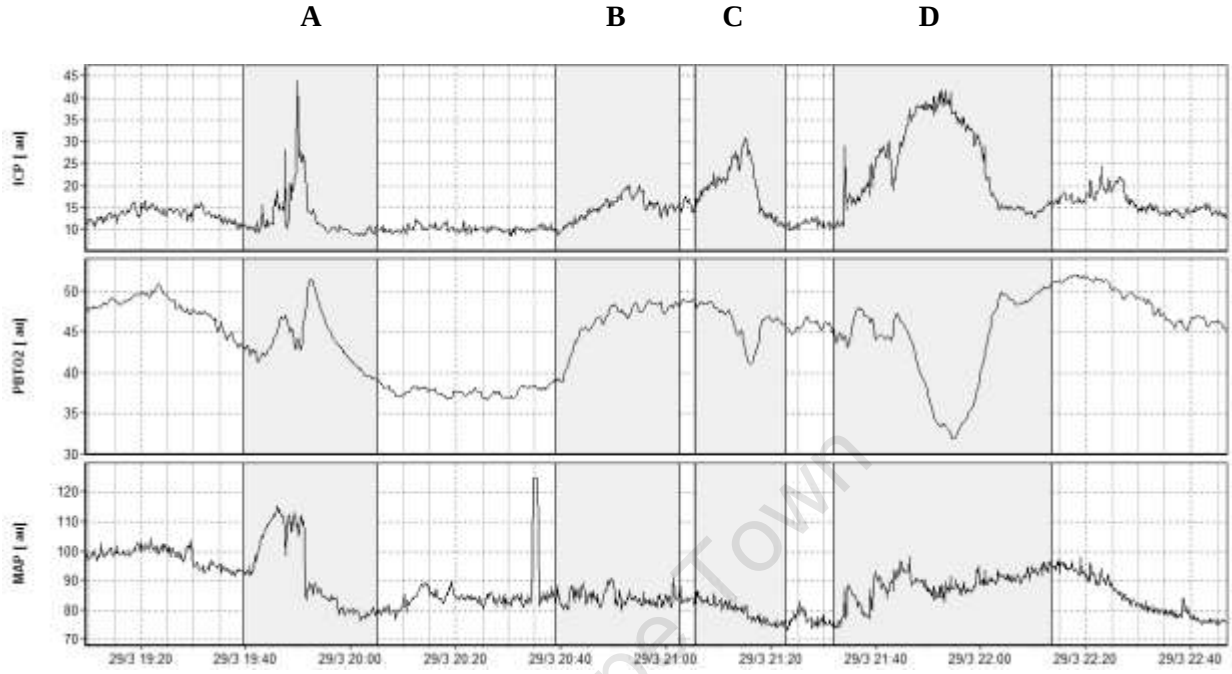
Impaired pressure autoregulation



The complex interplay between ICP and PbtO2: Figure 21 represents a summary of the possible ways in which ICP, PbtO2 and MAP may interact in a single patient over a restricted period of time; *A* denotes an impaired autoregulatory response, *B* demonstrates a positive relationship between ICP and PbtO2 which changes its course at *C* where ICP seems to have passed a critical point at which PbtO2 begins to decline. *D* indicates a negative relationship between higher ICP and PbtO2 under conditions of relatively constant MAP.

Figure 21

Complex relationship between ICP, PbtO2 and MAP



7. Data Capturing

A total of 216 hours (selected from a 24 hour period) were used for the ICP and PbtO2 analysis of manual versus electronic data collection methods.

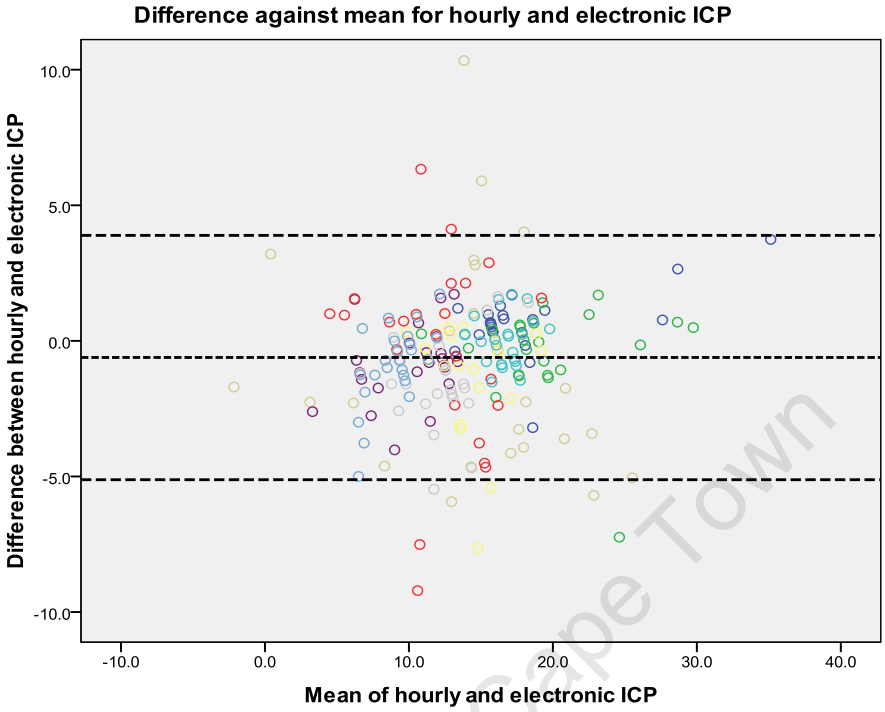
Mean hour

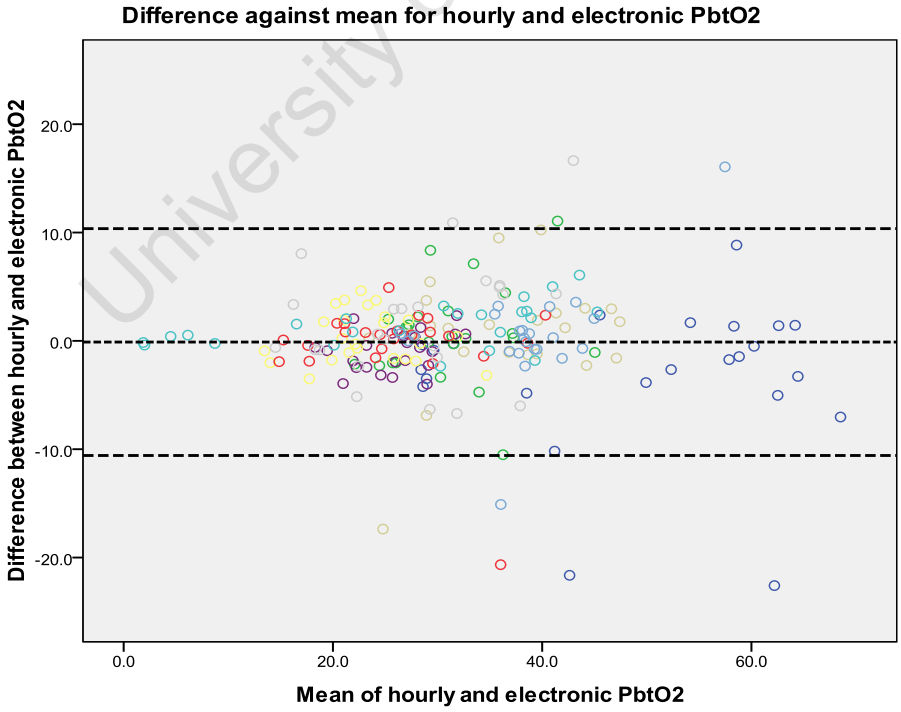
Bland Altman graphs for mean-hour ICP and PbtO2 electronic and hourly data are shown in Figures 22 and 23. Approximately 95% of all values for ICP and PbtO2 fell within the limits of agreement. The mean difference for ICP was -0.62 ±2.3 mmHg and -0.11 ±5.34 mmHg for PbtO2 (calculated as hourly – electronic). This suggests that approximately 95% of electronic and hourly data do not differ by more than 4.51 mmHg for ICP and 10.47 mmHg for PbtO2.

Distribution for mean-hour data was random about the mean, and did not present any trends which might suggest that values in the two techniques may differ in terms of level, with one consistently reporting higher or lower values than the other. There was also no indication that the difference between readings of these two techniques demonstrated different patterns for high values in comparison to low values.

Figures 22 and 23

Bland and Altman graphs for mean hour ICP and mean hour PbtO2





Number of episodes of high ICP and low PbtO2

Of a total recording time of 1364 hours for 9 patients, 452 episodes of ICP > 20 mmHg for ≥5 minutes were recorded digitally (33%), and 253 episodes hourly (18.5%). The difference in these proportions was significant (*z=8.91*) suggesting that high frequency recording captured a more detailed account of the profile of ICP. The number of episodes of PbtO2 <20 mmHg recorded electronically was 224 (16.4%), and 219 hourly (16%). There was no significant difference between these proportions suggesting that hourly and high frequency data gave a similar indication of the PbtO2 profile.

Chapter 9

DISCUSSION

This study examined time-linked ICP and PbtO2 observations in a cohort of 75 children with severe TBI (mean age 6.4 years, median GCS 6). This is an important topic considering that ICP treatment is the cornerstone of care for severe TBI in most centres. The purpose of treating ICP is to preserve brain oxygenation or perfusion and to avoid herniation, but evidence suggests that cerebral ischemia may occur despite ICP control and stable cardiorespiratory physiology. Different methods of brain oxygenation monitoring exist, and although measures of compromised brain oxygenation, like low PbtO2, appear to be strongly associated with poor outcome, often none of these monitors are used. Therefore, a better understanding of the relationship between ICP and PbtO2 would appear to be of relevance, particularly for children, in whom much less in known about both ICP and PbtO2.

The main findings of this study were that the relationship between ICP and PbtO2 is poor, and is variable between different patients and at different times. Several methods of analysing the data were employed, including correlation of all pooled data, controlling for inter-individual differences, controlling for other influencing variables, calculation of sensitivity and specificity of critical thresholds for ICP with PbtO2 as the outcome variable, construction of ROCs for ICP and PbtO2 (while taking 3 age bands into account), construction of ROCs for individual patients, and exploration of electronic data for case illustrations of the continuous relationships between ICP and PbtO2. The pattern of the relationship between ICP and PbtO2 is consistent across all of these analyses. This is likely because 1) there are several other variables that influence PbtO2, and 2) although high ICP has a negative influence on PbtO2, other factors (e.g. hyperaemia) may cause changes in ICP and PbtO2 that occur in parallel. Further confounding this relationship may be the inclusion of several age ranges in which the physiological norms are rapidly changing and for which we do not have clarity for optimal specific ICP and CPP thresholds for management.

ICP and PbtO2 profiles following pTBI

Despite attempts to adhere to treatment thresholds for ICP and PbtO2, perturbations in these variables were frequent in this patient group. Episodes of PbtO2 < 20 mmHg were seen in 66% of patients, almost 47% experienced PbtO2 < 10 mmHg, and 18.7% experienced levels

< 5 mmHg. ICP > 20 mmHg occurred in 84% of the children, and over half had episodes of ICP > 30mmHg. These data confirm the high prevalence of secondary intracranial hypertension and cerebral hypoxia/ischemia following paediatric severe TBI.

The time-course for ICP and PbtO2 in this study resembles that of other studies, with elevated ICP and reduced PbtO2 occurring most commonly early after injury, but with some delayed intracranial hypertension and cerebral hypoxia also present. Temporal patterns of PbtO2 and ICP derangements were similar but their values opposite, as expected. The progressive decrease in ICP over the first 5 days was accompanied by a progressive increase in PbtO2 over that time. The largest decrease in ICP and largest increase in PbtO2 both occurred between days 1 and 2. The highest mICP and lowest mPbtO2 were recorded on day 1, the lowest mICP and highest mPbtO2 were seen on days 5 and 6, and by day 3 over 60% of patients had experienced their peak ICP and lowest PbtO2. However, for individual patients ICP_{peak} and $PbtO2_{low}$ were not necessarily related. The average difference in the days between ICP_{peak} and $PbtO2_{low}$ was 2 days, range (0-13 days). Even when the largest differences of 9 and 13 days were excluded, the mean difference was still 1.74 days.

The decrease in ICP and increase in PbtO2 over time after the injury probably reflect the normal course of patient recovery. The median time for monitoring was 5 days, by which time most patients had experienced their highest ICP and lowest PbtO2 values and were becoming more stable. Delayed intracranial hypertension may be due to events such as delayed cerebral oedema. While this is a potential cause of delayed cerebral hypoxia, additional factors like polytrauma may also be a source of late desaturation, as in the case of progressively deteriorating respiratory injury. Injury severity is also an important factor that can significantly affect the time course of all cerebral variables independently of each other, where prolonged perturbations in ICP and PbtO2 are functions of the extent of the primary injury and its immediate aftermath rather than being directly linked to each other.

It must also be considered that these profiles have been derived from hourly values. A more accurate manner of assessing the time course of ICP and PbtO2 may be in the investigation of electronic high frequency data which provides a complete picture of their tends across time. However, hourly recordings appear to approximate averages for observations within the hour (see below).

It is possible that a phase difference may occur in the time course of changes for ICP and PbtO2, however attempting to conduct the analysis in consideration of this would be beyond the scope of this project and could be an objective for work in the future.

The time-linked relationship between ICP and PbtO2

Based on the rationale of improving brain oxygenation by ICP monitoring and control, it would be reasonable to anticipate that ICP has a significant negative linear relationship with PbtO2. Analyses using a very large number of observations, adopting several statistical methods and controlling for several potentially confounding variables did not demonstrate this, but revealed only a very weak relationship between ICP and PbtO2. This even had a positive slope in the initial part of the scatter plot, only becoming negative at higher values of ICP. While this was a statistically significant result, this may be due to the very large number of data observations. Moreover, it is essentially the r-value which is clinically important as it indicates the strength of association between ICP and PbtO2, which was in this case weak (r = 0.05). Although this would seem to suggest that ICP has little overall negative impact on brain oxygenation, especially below thresholds or with mild to moderate intracranial hypertension, these results should be interpreted with caution and it should not be assumed that the relationship between ICP and PbtO2 is straightforward. Similar to the studies of ICP-directed treatment versus CPP-directed treatment [106] it may be worth examining ICP and PbtO2-directed treatment. Presently, a phase II trial of PbtO2-directed treatment is planned in adults, but nothing is planned in the paediatric population to our knowledge.

Exploring critical threshold values of ICP and PbtO2

ROCs did not show high diagnostic accuracy for any of the levels of ICP in detecting low brain oxygenation (tested at various thresholds of low PbtO2) and were poorest for PbtO2 = 20 mmHg. Taking age bands into consideration did not improve the demonstration of a relationship between high ICP and low PbtO2. All the ROCs constructed for pooled data were generally poor; not an unexpected finding given the poor correlation observed between ICP and PbtO2. ROCs for individual patients confirmed that the relationship between ICP and PbtO2 is complex, and that it is probably influenced by several factors of physiology and pathology that differ between individuals.

The sensitivities and specificities of differing levels of ICP for varying levels of PbtO2 were investigated in order to evaluate whether they would resemble or support ICP treatment at the currently recommended threshold. In general, as the ICP threshold increased, sensitivity decreased (accounted for by the decreasing proportion of total hypoxic episodes for increasing ICP thresholds), but specificity increased (due to the fact that the number of

hypoxic episodes accounted for a larger proportion of all the PbtO2 observations as ICP increased). These sensitivities and specificities indicate that the recommended ICP threshold of 20 mmHg detected 42% of episodes of PbtO2 < 10 mmHg and 29% of PbtO2 < 20 mmHg. As may be expected, a lower threshold of ICP captured more episodes of low PbtO2, with ICP of 15 mmHg detecting 61% of PbtO2 < 10 and 51% of PbtO2 < 20 mmHg. This does not suggest that treating ICP at 15 mmHg would avoid these additional episodes of low PbtO2, since they may merely reflect brain hypoxic/ischemic episodes unrelated to ICP, or the fact that a greater number of observations fell into lower ICP threshold categories (i.e. there were more observations for ICP>15 than for ICP>20). These sensitivities indicate that ICP thresholds of 20 mmHg and 15 mmHg essentially miss between 40% and 70% of all cases of low PbtO2 (PbtO2 < 10 and < 20 mmHg). This reiterates the important point that other factors are responsible for compromised brain oxygenation in as much as 60% of cases of cerebral hypoxia.

Although a larger proportion of PbtO2 values were low as ICP increased, even when ICP was substantially increased, PbtO2 was not necessarily decreased in all patients. For example, when ICP was greater than 40 mmHg (n=85, Table 6), over half of the PbtO2 observations were still greater than 20mmHg. However, it is important to note that this may reflect the effectiveness of PbtO2 intervention. Age-related thresholds detected 90% of cases of low PbtO2, which may merely reflect that these thresholds for ICP are relatively low. The specificity was less than 20%.

From these analyses no single critical threshold of ICP demonstrated a marked effect on sensitivities and specificities for low PbtO2, but the relative risks for low PbtO2 increased progressively as the ICP threshold increased, mainly for PbtO2 < 10 and PbtO2 < 5 mmHg . Therefore, while it is clear that high ICP does pose a risk for lower PbtO2, there is substantial variability about this relationship, and no particular threshold indicated by these results. These are important findings, especially for children in whom less is known about optimal ICP treatment thresholds, but who have substantially lower ranges for ICP in health. It is still possible that lower thresholds for treating ICP should be considered for children, however these data to not clarify that threshold, and further study would be needed. What may be useful is a comparison of these results with similarly analysed data from an adult population.

Why is the relationship between ICP and PbtO2 variable and what are the implications?

There are several possible ways in which ICP and PbtO2 may interact. First, high ICP may directly cause low PbtO2 due to decreased CPP and/or tissue pressure effect. Second, a third factor may negatively affect both ICP and PbtO2 simultaneously. This does not preclude that the increase in ICP will in turn have a negative effect on PbtO2 after reaching a critically high level, but emphasizes that it is not the only factor causing a decrease in PbtO2. Possible third factors include:

1) Brain swelling: Tissue swelling is an important cause of raised ICP following TBI. Simultaneously oedema could cause an increase in the diffusion distance of oxygen from the capillary to the cell, thereby leading to a decrease in PbtO2.

2) Hypotension: Poor cerebral perfusion brought on by systemic hypotension potentially leads to cerebral ischemia, cell swelling and tissue oedema, which may in turn result in an increase in ICP. Once again the increase in ICP accompanies a drop in PbtO2 but is not necessarily the direct cause thereof.

3) Injury severity: Both raised ICP and low PbtO2 may reflect injury severity. The more injured the brain, the greater the perturbation in cerebral physiology. This is associated with not only a greater likelihood of ICP and oxygenation problems, but also a stronger probability of other complications, like impaired pressure autoregulation and vascular reactivity, poor cerebral perfusion and disturbed metabolic function. This combination of global injury could exercise further negative impact on ICP and PbtO2.

Third, a factor may cause an increase in both ICP and PbtO2, such as hyperaemia, hypercarbia, and increased blood pressure when pressure autoregulation is impaired.

Fourth, the factor affecting PbtO2 may have no association with ICP. The most overt of these are changes in blood pressure and systemic oxygenation (respiratory physiology and haemoglobin). However, some of these episodes of low PbtO2 occur even when blood pressure and systemic oxygenation appear to be adequate [41], suggesting that other variables that are not commonly measured may also cause low PbtO2. It follows that treating only ICP in order to ensure adequate tissue oxygenation, without actively monitoring some form of brain oxygenation may consequently leave some hypoxic insults untreated.

Therefore, although treating ICP is likely to remain an important goal in TBI management, it is important to note that the correlation between ICP and PbtO2 is poor. This may be of

greatest relevance to centres where no form of brain oxygenation is monitored. Given that episodes of low PbtO2 are independently associated with outcome in severe paediatric TBI, and perhaps even more strongly than ICP in certain circumstances, episodes of low PbtO2 in the absence of high ICP are likely to be clinically important.

However, an interesting question arises regarding how to approach treatment of ICP, and in particular at what threshold, when PbtO2 is not compromised. Unnecessary treatment of ICP may have potentially adverse effects, while not treating ICP in the face of normal appearing PbtO2 may lead to delayed negative consequences if ICP were later to become uncontrolled. To exemplify, sustained hyperaemia may be associated with high ICP but adequate levels of PbtO2; if left untreated this may eventually lead to increased vasogenic oedema later in the patient's course, and a more significant rise in ICP that would impair PbtO2. Currently recommended thresholds for ICP treatment are based on studies performed in the early 90's and while these may still be relevant, it would be reasonable to re-examine these thresholds in the light of modern technology now being used to manage brain trauma. This would be of particular value in children for whom there is little evidence elucidating appropriate thresholds for ICP treatment given their unique and changing physiological profiles.

Of course it must be borne in mind that PbtO2 is highly variable and represents oxygenation in a very focal area of the brain; consequently, there is some uncertainty about how well this can be extrapolated to other areas of the brain. However, there is some data to suggest that relative PbtO2 changes represent global changes in oxygenation when the PbtO2 catheter is placed in normal appearing brain in patients with diffuse injury where there are no focal contusions [23, 113]. Additionally, while ICP may represent a more global cerebral phenomenon there may still be regional differences in the pressure gradients experienced. Therefore, although brain oxygenation monitors offer a focal measure, based on the fact that the PbtO2 and ICP catheters are placed ipsilaterally in close proximity to each other it is likely that their measurements are reflecting the pressure and oxygenation status of the same tissue area.

It is also important to recognise that cerebral pathophysiology is not static, but highly dynamic and variable, changing from one day to the next in a single patient, and displaying a very different picture from one patient to the next. Additional to ICP and PbtO2 there are several other variables that also have unique profiles and effects across time and individuals. Although the GEE attempted to account for inter-individual variation for both ICP, PbtO2 and the other controlled variables, none of these variables stand alone, and it is their combinations which may be unique to individual patients and which may change the

pathophysiological picture substantially, making it difficult to outline an average picture of cerebral pathophysiology in TBI.

These findings suggest that PbtO2 reflects dynamics which are determined by several variables, not all of which can be easily measured. Strong associations were not found between PbtO2 and the other controlled variables. However, in individual patients it is also clear that variables such as PaO2, PaCO2, BP and Hb may affect PbtO2 dynamically, similar to the isolated changes in ICP seen in the case illustrations of this study. When analysing pooled data, this association may be lost. This may once again also be influenced by the fact that these patients were routinely treated for perturbations in any of these variables, such as hypotension, hypoxia, hypercarbia, and anaemia. CPP was found to correlate better with PbtO2 than ICP; since CPP is derived from both MAP and ICP, it has been suggested that it may better reflect the influence of MAP and ICP on PbtO2 [29]. Further study on CPP and brain oxygenation may better elucidate the nature of these relationships.

Case Illustrations

The trends selected in this section of the results illustrate the complexity of the relationship between ICP and PbtO2, but also how strongly increased ICP may reduce PbtO2 in specific circumstances. Positive relationships between ICP and PbtO2 are seen in conditions of hypercarbia, hyperaemia or impaired pressure autoregulation. However, even when ICP and PbtO2 increase in parallel, if ICP passes a particular threshold, it may begin to impede PbtO2. What this level may be is clearly not yet well understood, and it may indeed vary between individuals and over time.

Data Capturing

A comparison between electronic high frequency and hourly recordings of ICP and PbtO2 suggests that over 93% of data points fell within a methodologically acceptable level of agreement. This is similar to findings by Zanier et al [145]who found that 96% of hourly and electronic data fell within the limits of agreement.

While it appears as if electronic and hourly data may be used interchangeably with a certain degree of confidence, it is important to note that the electronic values analyzed for mean-hour comparison were averaged over one hour. As the case illustrations suggest, significant relationships between variables like ICP and PbtO2 occur over short durations of only a few

minutes and can be camouflaged when averaged across time. The outliers seen in the graphs comparing electronic and hourly recordings are indicative of this phenomenon: large spikes or continuous fluctuations in either ICP or PbtO2 may go completely unnoticed when they occur off the hour, but significantly alter the electronic means which take them into account. This was reflected in the comparison of high ICP episodes in which hourly recording missed almost 15% of episodes captured digitally. The fact that these two recording techniques did not differ significantly in terms of episodes of PbtO2 < 20 mmHg may be due to the fact that unlike ICP which has a tendency to spike transiently, PbtO2 values fluctuate with less frequency and intensity, returning more gradually to baseline after a drop or rise.

Although conducted with only a small sample, these results give indications about the respective capabilities of these two recording techniques. While manual hourly recording appears to provide a reasonably accurate account of physiological progress it may fall short of demonstrating insult severity. Electronic high frequency data may therefore be preferable in the assessment of cerebral variable profiles and would allow the investigation of pathological events, such as intracranial hypertension, in terms of time, frequency, depth and duration.

While hourly data may miss some important relationships, analysis examining the relationship between ICP and PbtO2 in this study was conducted using time-linked readings, which were both recorded hourly and simultaneously. Therefore the association of ICP and PbtO2 holds true at those designated time points.

Study Limitations

There are several limitations of this study which should be considered. First, this cohort was composed of patients for whom ICP and PbtO2 were constantly being observed and managed and for whom the thresholds of ICP < 20 mmHg and PbtO2 > 20 mmHg were being targeted. Various interventions were employed which may have influenced these results, and untreated ICP and PbtO2 may demonstrate different relationships, particularly at higher values of ICP. PbtO2 and ICP values beyond the recommended thresholds occurred in relatively small proportions, for example, PbtO2 < 10 mmHg accounted for only 155 observations from a total of 8389 observations. Different results may have been seen with untreated ICP and PbtO2, however, this could never be ethically justified. The fact that the analyses conducted on ICP and PbtO2 compared time-linked paired observations may overcome a degree of this limitation, with the exception that it is likely active treatment

reduced the relative proportions of high ICP and low PbtO2. Had terminal data not been removed from these analyses the relationship between ICP and PbtO2 may have appeared stronger, however, this is a study conducted on children that were well enough to treat, the results of which may be of relevance to patients being treated in the usual clinical context.

Second, although age was considered in 3 'bands', the rapidly changing physiological profiles exhibited by a paediatric population make the accurate evaluation of ICP very challenging. Also, very little data was available to guide the selection of which thresholds were appropriate for these age bands. Optimal treatment thresholds for different age groups are still not known, and it is possible that better identification of specific ICP thresholds for each age may improve the analysis. Additionally, although open sutures or fontanels in younger children could potentially create a different picture of intracranial dynamics, children under the age of 2 years were included in the overall correlation analysis. This was based on the fact that in general this cohort was composed of a very large age range of children (4 months – 14 years), all of whom may differ from each other in anatomic and physiological characteristics across the age spectrum. The correlation was however repeated using only patients over the age of 2 years, but this did not improve the demonstration of a relationship between PbtO2 and ICP ($r = 0.045, p < 0.01$) The scatter plot is included in Appendix B. While study of smaller age bands would provide valuable information this would require a very large number of patients per age category and would be specific to narrower patient groups. This cohort represents the heterogeneous composition of patients that would be seen in the context of paediatric TBI and allows for some generalizability of results to this patient population as a whole and who are treated according to standard guidelines regardless of age. This study is also a first step in identifying potential issues which can guide further studies on more defined and homogenous patient groups.

Third, while all values of PbtO2 and ICP were time-linked and therefore comparable, use of hourly data may have been limited. Analysis of data from individual patients with high-frequency data collection did however reveal several different clinical scenarios depicting varying relationships between ICP and PbtO2. ROC's constructed in individual patients with these high frequency data points also suggest that in some cases ICP and PbtO2 have stronger relationships, while in others this relationship is weak.

Finally, no monitoring modality is without its limitations or presents the full picture. Although PbtO2 appears to be a useful tool for monitoring an aspect of brain oxygenation, it is still not a precise measure of the adequacy of brain oxygenation. In particular it is sensitive to several other variables, especially arterial PaO2. It is possible that a similar study using

jugular venous saturation and near-infrared spectroscopy may produce different results but this is thought to be unlikely. PET is the gold standard for measuring brain perfusion, but can only be done as a 'snapshot' study at one point in time. Transcranial Doppler (TCD) produces data on velocity from vessels of the Circle of Willis and approximates changes in CBF relatively well. However, it is very difficult to perform TCD continuously in a reliable manner. Local CBF measurement, for example with a thermal diffusion probe, may provide some further insights on this topic. Still, very little data exists on the relationship between ICP and measures of brain oxygenation, particularly for children; therefore these data are useful to inform further study on the subject. Furthermore, although ICP was used as a surrogate of cerebral venous pressure (CVP), ICP and CVP have been shown to exhibit a good correlation, and considering the challenge involved in measuring CVP directly, ICP is widely used as an acceptable indicator of CVP in perfusion assessment.

It should also be mentioned that although the mechanism of injury in non-accidental injury (NAI) is unique and may potentially create a different pathophysiological picture, the two cases of NAI were included in analysis for the following reasons; firstly; while it is possible that the pathophysiology of TBI may differ based on the mechanism of injury, our cohort was heterogeneous in the manner by which they were injured, as is usually the case for TBI studies. Arguably, there are several mechanisms of injury that may produce unique patterns of pathophysiological disturbances. Therefore, if the mechanism of injury were to be taken into account in our analysis, this would require subdividing our patient cohort into several categories of injury beyond merely NAI. As much as it is true that this analysis would produce a more accurate result; this would require a very large number of patients per category, which is difficult to achieve in a single centre study. Secondly, current treatment guidelines are standard regardless of mechanism of injury with the underlying assumption that pathophysiological principles are the same across all TBI patients. While this may not be entirely appropriate it is the framework within which patients are being managed, and the results of this analysis are intended to be of value to the entire treating population. Thirdly, while ICP and PbtO2 certainly exhibit a relationship this relationship may demonstrate variability; mechanism of injury may be a factor to contributing to this, however it is also only one of many.

Future Research

The results of this study strongly suggest the need for more research directed at understanding brain oxygenation, its determinants, the dynamics which affect it, and how it

relates to global brain damage in the context of paediatric TBI. This would enable better prediction of how PbtO2 will be affected by intracranial and systemic pathophysiological changes, would provide greater insight into the nature of the interaction between PbtO2 and other relevant variables, would allow better precision of critical threshold points that can be tolerated and that should indicate treatment and would assist in targeting treatment more appropriately. These are important to improve the use of ICP monitoring, which is widely practiced. Specifically, further study is required on optimal ICP thresholds in children. Retrospective examination of ICP patterns in children who die may only reflect ICP in the terminal phase of the patient's clinical course, or the confounding association of mortality and high ICP with increased severity of disease, rather than the adverse effect ICP itself has on causing neurological compromise or death. If age is to be taken into account, this requires large numbers of patients. Given the relatively small numbers of children with severe TBI seen at individual centres, this would require a multicentre study. Similar study would have to be done for thresholds of MAP/ CPP with age. Comparison of similar data derived from a study of adult patients may be useful to detect differences in the relationship between various ICP thresholds and brain oxygenation.

Chapter 10

CONCLUSION

This study demonstrates that the relationship between ICP and PbtO2 is complex. While ICP does negatively affect brain oxygenation, several other factors may also be important in individual patients and at different times. Consequently, optimal approaches to ensuring the adequacy of brain oxygenation should take into consideration not only ICP, but a complement of relevant variables, and should ideally include some form of brain oxygen or perfusion monitoring. Further research into understanding other significant factors that influence PbtO2 and mediate the relationship between ICP and PbtO2 would be of great value in informing treatment strategies directed at avoiding secondary cerebral ischemia/hypoxia with the hope of improving outcome after TBI in children. In addition, more investigation into optimising ICP thresholds for treatment in children is needed. The use of complimentary monitoring modalities may assist in this task. Depending on the adequacy of measures of brain perfusion, metabolism or oxygenation, it is possible that targeting a range of ICP values in individual patients may be appropriate; however this would require detailed investigation.

APPENDIX A: PATIENT MANAGEMENT

General

Management of ICP and CPP at Red Cross Children's War Memorial Hospital is broadly in keeping with the Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents [2]. Significant intracranial haematomas were surgically evacuated as soon as possible, ICU treatment aimed to avoid systemic hypoxia and hypotension, and ICP, CPP, and PbtO2 were actively managed. Baseline patient management involved 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 an intraparenchymal monitor (Codman ICP Express [Codman, Raynham, MA] or Camino [Integra Neurosciences, Plainsboro, NJ]) or a ventriculostomy device. Sustained ICP > 20mmHg was treated actively. In the case of intracranial hypertension, head CT scanning was performed to rule out delayed 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 pressure autoregulation. When ICP was elevated despite these baseline measures, increased sedation, neuromuscular blockade, ventriculostomy, controlled moderate hyperventilation, and/or hyperosmolar therapy (5% saline and/or mannitol) were employed in a stepwise fashion.

Controlled moderate hyperventilation (PaCO2 28 to 30mmHg) was infrequently used and only for brief periods as a second-tier therapy to treat intracranial hypertension. It was used in conjunction with transcranial Doppler (TCD) and PbtO2 measurements, and only if PbtO2 was greater than 20mmHg. Hypertonic saline was used to treat elevated ICP if the serum sodium was < 155 mmol/L. Thiopentone was used for elevated ICP refractory to standard treatment on condition that the patient's blood pressure (BP) was stable. Decompressive craniectomy was used as a second-tier therapy in cases of refractory elevated ICP which did not respond to thiopentone or for rapidly deteriorating ICP control where ICP increased to ≥ 40mmHg or BP was too unstable for thiopentone. Occasionally, decompressive caniectomy

was used as an emergency when patients were admitted with gross brain oedema and increased ICP with signs of cerebral herniation.

CPP Management

Management of CPP was based broadly on the paediatric guidelines [5] which recommend maintaining CPP > 50mmHg, while taking into account that CPP may vary based on patient age. 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, CPP management was influenced by the concurrent ICP and PbtO2 values, as well as TCD and autoregulation testing results when available. The first step in CPP management involved 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, MAP was elevated by administering noradrenalin or dopamine.

PbtO2 Management

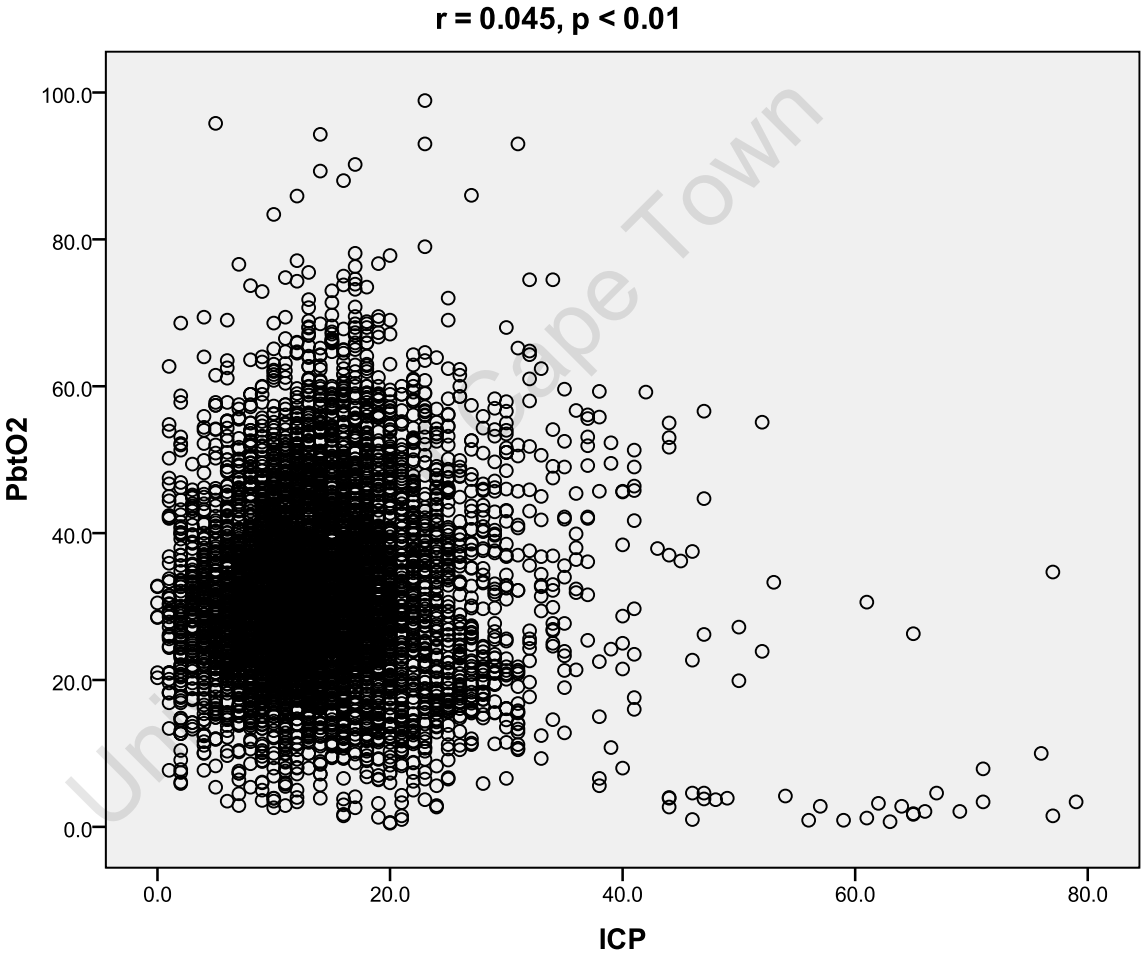
PbtO2 was measured with Licox catheters (Integra Neurosciences, Plainsboro, NJ), which were inserted into normal-appearing right frontal white matter if there were no localised lesions. Occasionally a second PbtO2 monitor was placed in a pericontusional location if the patient had what appeared to be a clinically significant large contusion (these data were excluded from analysis). Monitor location was confirmed on follow-up head CT. Compromised (low) PbtO2 was defined as <20 mmHg and was treated using a hierarchical treatment algorithm, which depended on the depth and duration of the reduction in PbtO2, and in which the cause of low PbtO2 was always sought and treated where possible. In the absence of detecting a specific cause the following measures were used depending on ICP, MAP, PaO2, Hb, PaCO2, TCD flow velocities and the 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 using volume infusion and/or inotropic support unless impaired autoregulation caused increases in ICP simultaneous 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 treating the above mentioned parameters. Where possible management aimed at individualising treatment for patients.

Ventilatory Management

Patients remained intubated and ventilated for the duration of intracranial monitoring. Ventilation was adjusted to maintain SaO2 > 95% and PaO2 approximately 13kPa (~100mmHg). PaCO2 was kept within the range of 4 to 4.5kPa (~30-35 mmHg).

APPENDIX B: CORRELATION ANALYSIS EXCLUDING DATA FROM CHILDREN UNDER THE AGE OF 2 YEARS

Having excluded all data for patients under the age of 2 years, Spearman's correlation was once again performed on the remaining ICP and PbtO2 data (6795 observations). The results of this analysis demonstrated that excluding the data on these children did not improve the demonstration of a relationship between ICP and PbtO2 *(r = 0.045, p < 0.01)*.



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