The prevalence of cerebral hypoxia/ischemia in pediatric severe traumatic brain injury

Dissertation for Masters degree in Medicine (Neurosurgery)

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Abbreviations

ADC: Apparent diffusion coefficient

ATP: Adenosine Triphospate

ADP: Adenosine Diphosphate

AIDS: Acquired Immune Deficiency Syndrome

ANLS: Astrocyte-neuron lactate shuttle

$AVDO_2$: Arterial-venous difference in oxygen saturation

BBB: Blood Brain Barrier

CBF: Cerebral Blood Flow

CBV: Cerebral Blood Volume

CCT : Central conduction time

CMR_{GLUC}: Cerebral metabolic rate of glucose consumption

$CMRO_2$: Cerebral metabolic rate of oxygen consumption

CO_2: Carbon dioxide

CPP: Cerebral Perfusion Pressure

CSF: Cerebrospinal Fluid

CvO_2: Cerebral venous Oxygen content

DWI: Diffusion weighted imaging

EAA: Excitatory amino acids

EDH: Extradural Hematoma

EEG: Electroencephalogram

FDG: Fluorodeoxyglucose

H+: Hydrogen

HBO: Hyperbaric Oxygen

HIV: Human Immunodeficiency Virus

^{1}H MRS: Proton Magnetic Resonance Spectroscopy

IBV: Ischemic Brain Volume

ICA: Internal carotid artery

ICH: Intracranial Hematoma

ICP: Intracranial Pressure

ISF: Interstitial Fluid

K+: Potassium

LPR: Lactate Pyruvate Ratio

MAP: Mean Arterial Pressure

MCA: Middle Cerebral Artery

Mhz: Megahertz

MTT: Mean transit time

NIRS: Near Infrared Spectroscopy

$PaCO_2$: Partial pressure of arterial carbon dioxide

$PbtO_2$: Brain tissue oxygen tension

PWI : Perfusion weighted imaging

PET: Positron Emission Tomography

PI: Pulsatility index

PaO_2: Partial pressure of oxygen

PRR: Pulse Repetition Rate

PTCI: Post Traumatic Cerebral Ischemia

rCBF: Regional cerebral blood flow

RBC: Red Blood Cells

ROI: Region of interest

SAH: Subarachnoid Hemorrhage

SaO_2: Oxygen Saturation

SDH: Subdural Hematoma

$SjVO_2$: Jugular Venous Oxygen Saturation (Jugular Venous Oximetry)

SNR: Signal to noise ratio

SSEP: Somatosensory evoked potentials

Tb: Transmitted sound burst

TBI: Traumatic Brain Injury

TBV: Total Brain Volume

TCA: Tricarboxylic acid cycle

TCD: Transcranial Doppler

TOI: Tissue Oxygen Index

Viz: namely

V_s: Peak systolic velocity

V_d: Peak diastolic velocity

V_m: Time-averaged mean velocity

Xe-CT: Xenon-enhanced computed tomography

Glossary

Autoregulation: A physiological mechanism by which the brain regulates and maintains adequate cerebral blood flow to the parenchyma.

Diaschisis: A reduction in neurometabolic activity remote from the infarct site, due to the disconnective effects of the infarct, with loss of afferent signals to other regions of the brain.

Hypoxia: A reduction in tissue PO_2 to levels insufficient to maintain cellular function, metabolism and structure.

I**ncidence**: The number of new cases of a disease in a defined population over a specific period of time.

Infarction: Sudden insufficiency of arterial or venous blood supply due to emboli, thrombi, vascular torsion, or pressure that produces a macroscopic area of necrosis.

Ischemia: Inadequate circulation of blood to sustain normal tissue function, structure or metabolism.

Metabolic crisis: The elevation of the lactate/pyruvate ratio (LPR) > 40, seen after severe TBI (142) – this is a microdialysis based definition, as reflected by abnormal cerebral microdialysis LPR, in the context of TBI. This definition is differentiated, contextually, from other definitions of metabolic crisis, which usually relate to inborn errors of metabolism often associated with mortality in neonates.

Penumbra: Area immediately surrounding a region of vascular compromise.

Perfusion: Tissue blood flow or blood flow in the microvasculature. This is the rate which the quantity of blood in a given mass or volume of tissue is replenished at the level of the capillaries. Perfusion is often given in the units ml/100g/min.

Pressure-passive flow: A pathological situation where CBF is passively determined by MAP due to failure of autoregulation.

Prevalence: The number of cases of a disease existing in a given population at a specific period of time or at a particular moment in time.

Primary injury: Injury sustained at the point of impact, damage is usually irreversible.

Secondary injury: Injury sustained after the initial insult, may be prevented and is often reversible.

Thermal conduction: The ability of a solid medium, such as tissue , to transport heat (thermal energy).

Thermal convection: The ability of a fluid medium, such as blood, to transport heat (thermal energy).

Thermistor: An electrical element that changes its resistance in response to a temperature change.

Voxels: A contraction for volume element, which is the basic unit of CT reconstruction, represented as a pixel in the display of the CT image.

CHAPTER 1: INTRODUCTION

Severe traumatic brain injury (TBI) is a major cause of mortality and disability in both adults and children. While most of these injuries in children may be mild, any injury to the developing brain is important because it may still cause some degree of long-term deficit. Those who sustain severe head injury have a high mortality and survivors often demonstrate severe functional and cognitive impairment so TBI is a major health and socioeconomic concern (1, 2, 3). The incidence of TBI varies between 100 and 250 per 100 000 in western industrialized countries (5, 9, 10). However, TBI, and in particular, pediatric TBI continues to receive inadequate funding for both basic science and clinical research (4), especially when compared with funding for infectious diseases like tuberculosis and HIV/AIDS.

The outcome in head injury is not only related to the severity of the initial injury, but also to how well the patient is managed in the acute period following the injury, i.e. prevention of secondary injury (6, 7, 292, 293). Secondary injury includes hypoxia/ischemia, hypotension, hyperthermia, brain oedema, delayed intracerebral hematoma (ICH), dysautoregulation of cerebral vasculature, metabolic abnormalities, raised intracranial pressure, infection, seizures and extracranial causes eg. chest infection. Secondary injuries are important because they represent an opportunity for the treating physician to intervene and therefore to have an influence on outcome. In particular cerebral ischemia may be a major factor leading to poor outcome. It is well recognized that global cerebral blood flow (CBF) is lower in head injured patients when compared to age-matched controls (120, 122), and some have suggested that cerebral ischemia may be the single most important cause of secondary brain injury after severe head trauma (121, 122, 123, 124), supported by histological evidence that ischemic brain damage is common in most head injured patients who die (13, 14).

Alterations in CBF play a major role in the pathophysiology of severe head injury (7, 8, 12). Several factors influence CBF dynamically in head-injured patients. In TBI, one of the major determinants of CBF and hence perfusion of the injured brain is

cerebral perfusion pressure (CPP), which is the difference between mean arterial pressure (MAP) and intracranial pressure (ICP). CBF is usually controlled within a wide range of blood pressure changes by the capacity of the cerebrovascular bed to vary the diameter of the arterioles (pressure autoregulation). Disruption of the autoregulatory capacity in the head injured patient impairs the capacity of the brain to respond to changes in perfusion pressure and places the brain at higher risk of ischemia. Several other factors also affect CBF, including the metabolic activity of the brain, systemic changes in carbon dioxide (CO_2) and oxygenation, temperature and pH. Each of these factors may be influenced by therapies implemented in the ICU and may be relevant to the overall burden of ischemia.

Although it has generally been accepted that cerebral ischemia is an important factor influencing outcome from head injury, attempts to demonstrate where, why and how often true ischemia occurs in the brain, have stirred debate (11). In TBI, the issue is more complex than it is in stroke models. Accurate demonstration of ischemia in TBI has proved elusive, because regional reductions in CBF may actually represent areas of hypoperfusion, which are appropriately coupled to areas of hypometabolism (metabolic coupling). Most commonly quoted thresholds for CBF and cerebral oxygen metabolism ($CMRO_2$) are based on experimental studies of ischemia and clinical stroke, but these cannot necessarily be directly translated to TBI (23, 29, 32, 33, 39, 40).

There are currently various methods for measuring CBF, cerebral blood volume (CBV) and cerebral oxygenation, or surrogates of these, all of which have different strengths and limitations. These include techniques such as positron emission tomography (PET), xenon enhanced CT scan (Xe-CT), single photon emission CT (SPECT), perfusion CT, MRI sequences, transcranial doppler flow measurements (TCD), jugular bulb oxygen saturation ($SjvO_2$), near infrared spectroscopy (NIRS), brain tissue oxygenation ($PbtO_2$), thermal diffusion regional CBF measurements, microdialysis (MD), electroencephalography (EEG) and somatosensory evoked potentials (SSEP). None of these methods are independently able to effectively diagnose ischemia continuously in the neurocritical care unit. Therefore it is up to

the clinician to evaluate the strengths and weaknesses of each and use them appropriately in the clinical environment.

Several studies have reported ischemia after TBI (11, 13, 14, 15, 16, 17, 22, 139, 141, 142, 149, 159). The most compelling evidence supporting the occurrence of ischemia after TBI comes from early studies based on findings from autopsies of fatal TBI cases, which suggest a relatively high frequency (13, 14). Most of the ischemic damage demonstrated was found in well localized anatomical areas, including the hippocampus, basal ganglia and cerebellum. More recent evidence supporting a high frequency of ischemia post-TBI in antemortem studies were based on hyperacute studies of CBF, and $SjvO_2$ (11, 15, 16, 17). These findings have been confirmed by others over the past two decades (18, 19). However recent PET studies of cerebral ischemia after TBI have re-invigorated the discussion, with one study in particular suggesting that the frequency of true ischemia after TBI may actually be quite low (142). These PET studies are important to consider because PET is currently considered the gold standard for diagnosing complex vascular and metabolic alterations in the brain, including ischemia. However, PET studies have significant temporal limitations, and provide a snapshot of the brain at one particular time, whereas TBI is a complex, dynamic condition. Also, PET studies, can only be performed on patients who are relatively stable. On the other hand, continuous methods for measuring brain perfusion or oxygenation also have several weaknesses, in particular the focal nature of their monitoring capability. And so, in terms of monitoring or diagnostic strategies, the options we have available in TBI tend to fall into one of two categories: either 1) the method has good spatial resolution and is more specific, but can only provide a 'snapshot' of the brain at one point in time (poor temporal resolution), or 2) the method is continuous but is less specific and has limited spatial resolution. However, studies using methods from each of these two categories tend to generalize their findings. This is not always appropriate, especially given the inter- and intra-individual heterogeneity of TBI. In individual patients, TBI is a dynamic condition in which different parts of the brain may react differently depending on several underlying factors, and which changes over time, often dramatically.

Therefore the present study was undertaken to examine the comparison of a single method used both as a 'snapshot' modality and as a continuous one. A single method was chosen so that the comparisons would be appropriate. Even though the data from this study cannot be compared to other studies or extrapolated to other methods, it is a useful comparison of the type of information that one would obtain when a point-in-time method is used in comparison with continuous monitoring, and so may serve to provide greater insight into the dynamic nature of TBI.

For this purpose, $PbtO_2$ monitoring in children was chosen. The aim was to examine the frequency of low $PbtO_2$ at selected time points (which reflects the prevalence at those time points in this series) and compare these with the frequency of the same episodes calculated over the complete duration of monitoring (which better reflects the incidence of the condition).

The work is structured in 2 parts, the first part comprises chapters 1 to 4, which reviews the background to the topic, while chapters 5 onwards specifically address the present study. Specifically, chapter 2 reviews the important physiological concepts relevant to this thesis, chapter 3 describes the pathophysiology of cerebral ischemia in TBI, chapter 4 will discuss the methods of monitoring and measuring CBF, $PbtO_2$ and cerebral ischemia, and chapter 5 is a review of literature available on the subject. Chapter 6 will describe the study design and research methods used for this study and summarises the results.

CHAPTER 2: Relevant physiological aspects of cerebral blood flow and oxygen metabolism.

Some of the basic physiological mechanisms and principles involved in the regulation of cerebral blood flow (CBF), oxygen delivery (DO_2) and oxygen metabolism are discussed in this section.

Cerebral blood flow (CBF)

Average CBF (average between grey and white matter) is approximately 50-55ml/100g/min, representing about 20% of the cardiac output at rest, even though the adult brain represents 2-3% of the total body weight. The brain also uses 20% of the oxygen and 25% of the glucose consumed by the entire body. More than 90% of the oxygen consumed by the brain is used by mitochondria to generate ATP (124). However, CBF throughout the brain is heterogeneous, depending on the level of metabolic activity in the area and the type of tissue being measured. The flow rate to grey matter is about 70ml/100g/min, compared to 20ml/100g/min in white matter, due to the higher concentration of neuropils and synapses in grey matter. In general the rate of global CBF is kept relatively constant through cerebral pressure autoregulation.

Cerebral pressure autoregulation is a complex mechanism by which the brain controls and maintains adequate CBF through active constriction and dilation of cerebral arterioles to achieve a relatively constant substrate delivery to the brain. To maintain normal brain tissue substrate delivery, the brain has to regulate both regional and total blood flows at a fairly constant rate over a wide range of mean arterial blood pressures (MAP) viz. 50mmHg – 160mmHg (127). The adjustment in CBF is facilitated by vasoconstriction or dilatation of resistance vessels, which are approximately 200 micrometers in diameter. When MAP increases or decreases beyond these thresholds, CBF has a linear relationship with blood pressure;

therefore CBF may vary in a number of pathological conditions when 1) the normal limits of autoregulation are breeched, or 2) when autoregulation is impaired. Local CBF is also determined by various physical properties, as described in Virchow's triad of hemodynamic parameters for venous thrombosis, namely, the rate of blood flow, the status of the vessel wall and the blood coagulability (51). Some of these are represented in the Hagen-Poiseuille equation for general hemodynamics :

$$Q = \frac{\pi R^4 \Delta P}{8 \eta L}$$

Here, **Q** refers to blood flow, **R** refers to vessel radius, **ŋ** refers to blood viscosity, **ΔP** refers to change in pressure and **L** to vessel length, therefore blood flow varies proportionately with changes in vessel radius and inversely with blood viscosity (52).

It is important to appreciate that children and adults differ with respect to cerebral hemodynamics in the physiological and pathological state. The brain of a child is still developing and therefore reacts very differently to similar insults sustained in an adult. These variations occur for a number of reasons, which include anatomical differences (such as the size of the head relative to the body and open skull sutures) and physiological differences. The latter are due largely to processes of maturation and development, and include, variation in the amount of white and grey matter and variable water content, cerebral vasculature variations and incomplete white matter myelination, amongst many other features (53, 55, 56). While older studies did not take into consideration the developmental and gender-related differences in the physiological and cerebrovascular parameters of healthy children, recent data, mostly from TCD studies, suggest that CBF varies by age and gender (199, 200, 201, 202, 204, 205). TCD measures CBF velocity and not CBF directly, but changes in CBF velocity have been shown to correlate well with changes in CBF (203, 204). Gender-related differences in autoregulation and CBF velocity in the anterior and posterior circulation have been demonstrated (201). Vavilala et al, showed that girls between the ages of 10–16 years old demonstrated higher flow velocities in both the MCA and

basilar arteries than boys, while boys demonstrated greater autoregulation of the MCA and poorer autoregulation of the basilar artery than girls (201). These differences may be influenced by variations in blood viscosity, vessel size, cerebral metabolism or cerebrovascular resistance (202). TCD studies also suggest that CBF velocity increases with age until 6-9 years, with a decrease in CBF velocity after the age of 10 years (199, 200). Data from a PET study demonstrated that regional CBF (rCBF) in the < 1 year old age group is lower than in older children, with an increase in rCBF in infants, followed by a gradual decrease in adolescence to adult levels (273). A few reports have proposed that the 'excess' nerve cells and synapses produced during fetal development will start to denature and undergo a process of neural pruning, as part of normal development, occurring during the neonatal period and well in to adolescence (274 – 277). The remaining axons will undergo myelination, followed by rapid generation of synapses (275, 278, 279). Myelination begins in the fetal period, with a rapid increase in synaptogenesis in the neonatal period, peaking in childhood and continuing into adolescence. The aforementioned physiological correlations may explain some of the developmental changes seen in rCBF, as the increase in rCBF and regional cerebral metabolic rate of oxygen consumption ($rCMRO_2$) observed in the neonatal and early childhood periods would be necessary to sustain myelination and synapse development. There have also been reports of developmental, regional heterogeneity, where CBF was higher in the thalamus than in other brain regions at birth (280), more prominent in the occipital lobe between the ages of 1 and 4 years and highest in the frontal lobe over the age of 5 years (281). Ideally, many of these factors, if not all, should be taken into account when interpreting CBF and metabolic changes in pediatric TBI, given that cerebral hypoperfusion (CBF < 25ml/100g/min) appears to be a major physiological derangement that has been associated with poor outcome (11, 205, 206).

Local CBF and arterial oxygen content are the main determinants of oxygen delivery to brain tissue. It has been well documented that time-dependent neuronal events occur in response to a reduction in CBF (125, 126, 157, 159, 160). The brain has critical thresholds for CBF, which are fundamental to defining the thresholds for cerebral ischemia. A reduction in CBF to below 20ml/100g/min may lead to loss of

consciousness and slowing on the electroencephalogram (EEG), but may not always cause any lasting functional impairment. CBF below 5ml/100g/min lasting for more than 30 minutes, however, will cause brain infarction (160, 161) [These thresholds will be discussed in more detail in the next chapter]. Several factors affect CBF and exert these effects to varying degrees. These include cerebral pressure autoregulation, as described earlier, CO_2 reactivity, O_2 reactivity and various metabolic parameters, including pH and temperature.

Oxygen delivery (DO_2)

Atmospheric air comprises 21% oxygen, 79% nitrogen and trace amounts of CO_2. Oxygen is transported from alveolar air to blood, where it is carried by reversible binding to hemoglobin (Hb) and then transferred from blood to peripheral tissue by diffusion. Oxygen delivery (DO_2), denotes the total amount of oxygen delivered to the tissues per minute, and can be calculated by the equation :

$$DO_2 = 1.39 \times Hb(g/dl) \times SaO_2/100 \times Q/100,$$

where, 1.39 is the oxygen carrying capacity of hemoglobin (in ml/g /Hb), SaO_2 is the arterial oxygen saturation and Q is cardiac output (262). The oxygen – hemoglobin dissociation curve expresses the affinity of oxygen for hemoglobin. This curve may be shifted to the right or left and may be affected by several factors, which include those causing a shift to the *left*: decreased pH, hypocarbia, hypothermia, fetal Hb, carboxyhemoglobin, methemoglobin, decreased 2,3 DPG and those causing a shift to the *right*: increased pH, hypercarbia, hyperthermia and increased 2,3 DPG (262). The rate of oxygen delivery to peripheral tissue is dependent on the difference in oxygen partial pressure (PO_2) between capillary and the tissue cells. The physiology of oxygen distribution between the cerebral vasculature and brain, however, is still not completely understood (122). Constant oxygen delivery is required due to the high consumption of oxygen required to sustain mitochondrial activity. This process creates an oxygen tension gradient between the capillaries and the tissues, thus rendering the magnitude of oxygen flux vital to neuronal integrity. This is

important, because if blood flow stays constant, increasing oxygen transport to tissues may be achieved by increasing non-hemoglobin bound oxygen i.e. dissolved O_2. The importance of the dissolved oxygen tension is highlighted by the fact that many capillaries are smaller than red blood cell corpuscles, and therefore need to dilate in response to local tissue hypoxia, a process possibly mediated by the release of nitric oxide. There is also evidence from studies done on rat brain specimens, that suggests the existence of 'acellular blood flow' in the brain i.e. capillaries in the brain that do not contain erythrocytes (126).

Brain Oxygen Tension

Due to the consumption of oxygen in the tissue, brain tissue oxygen tension ($PbtO_2$) is best described as a continuum that can vary from close to 90mmHg, at points very close to capillaries, to much less than 34mmHg in more distal regions (128). It also depends on whether grey or white matter is being sampled. $PbtO_2$ can decrease to much lower levels in TBI where compromised CBF, decreased oxygen delivery and diffusion limitation in the tissues may occur. (128, 129). $PbtO_2$ was found to be closely related to the product of CBF and arteriovenous oxygen tension difference, suggesting that $PbtO_2$ is related to the diffusion of dissolved plasma oxygen rather than the total amount of oxygen released by hemoglobin (158). The demonstrated strong relationship between PaO_2 and $PbtO_2$ (67), is also the likely cause of increasing FiO_2 leading to increases in $PbtO_2$.

Brain Oxygen diffusion

Attempts have been made to describe quantitatively the diffusion of oxygen from blood to tissue as well as to define oxygen pressures in brain tissue (130, 131, 132). According to Fick's first law of diffusion, the driving force for O_2 diffusion is the difference in PO_2 between the two sites viz. from the vessels to the tissues, then eventually to the mitochondria. The development of a model describing tissue substrate delivery, which was based on the idea that tissues contain a parallel

arrangement of capillaries, each supplying a cylindrical volume of tissue, was initially suggested by Krogh in the early 1900's (133). He proposed that oxygen diffusion occurs radially from capillary blood to tissue and that oxygen consumption is constant over time throughout the tissue cylinder. Based on this theory, it follows that oxygen content in the proximal capillaries should be high and decreases linearly with the distance travelled along the vessel. While this model for diffusion has been widely applied and used by researchers, it has distinct shortcomings, which include the fact that oxygen diffusion is not limited to capillaries, but also occurs in precapillary vessels, and the fact that blood flow in these capillaries is not always unidirectional as was originally assumed (134). Even though our knowledge has improved significantly since those early years, no single existing theory has completely described oxygen transport from the vasculature to the cerebral tissue (135).

Cerebral metabolic rate of oxygen ($CMRO_2$) and glucose (CMR_{GLUC}) consumption.

The $CMRO_2$ of a conscious, normal human being is around 3,5ml/100g/min [approximately 20% of resting body O_2 consumption] (137). Under normal physiological conditions, the human brain consumes oxygen at a rate of 156 micromol/100g/min and glucose at a rate of 26-31 micromol/100g/min, assuming a respiratory quotient of 1 (1mole O_2 producing 1mol CO_2) (137). When the oxygen is delivered to the cell it is used in a variety of cellular reactions. Most oxygen is used in the generation of energy via the aerobic metabolism of glucose. It has traditionally been assumed that neurons and glia use glucose as their sole source of energy, but recent studies have demonstrated that some astrocytes and neurons show the ability to use a 'coupled lactate metabolism', where glucose is transported across the BBB, and is anaerobically metabolized to lactate (137, 21). Glutamate uptake in astrocytes induces a glycolytic response that provides at least some of the necessary cytosolic ATP to maintain both glutamate transport and allow its recycling by conversion to glutamine. This well known participation of astrocytes in the glutamate/glutamine cycle is essential to replenish the neuronal glutamate pool and maintain

neurotransmission (252). It has also been suggested by Cerdan et al (253), that lactate transfer between astrocytes and neurons occurring as part of the classic astrocyte-neuron lactate shuttle (ANLS) concept, serves not only the purpose of fueling the neuronal tricarboxylic acid (TCA) cycle but also provides reducing equivalents to the neuron. Thus the intracellular compartments of astrocytes and neurons are coupled and the transfer of lactate is determined by the redox state of each cell, predominantly oxidized in neurons due to the largely oxidative metabolism and reduced in astrocytes, because of the high glycolytic activity. The 'redox switch' described in this theory, also accounts for both the reduction in neuronal glycolysis and the favoured lactate utilization by stimulated neurons (253). It has also been demonstrated that astrocytes respond to extracellular glucose changes by altering their intracellular ATP concentrations, but hypothalamic neurons responded to changes in lactate levels instead (254). Therefore, improving energy metabolism by enhancing glucose uptake in astrocytes and lactate uptake in neurons, as suggested by the ANLS hypothesis, could represent a valuable neuroprotective strategy. (136, 137, 252).

Effects of oxygen on CBF

Although hyperoxia may improve the diffusion of oxygen through the tissues, less is known about the effects of oxygen on the brain compared with the known cerebrovascular responses to changes in blood pressure and CO_2, especially in the context of TBI. A reduction in perfusion due to vasoconstriction is a known response to prolonged hyperoxia, independent of the accompanying arterial hypocapnic effects (151). These responses may be mediated by nitric oxide. The cerebral vascular and tissue responses to hyperoxia may demonstrate regional differences associated with certain pathology (84). Unlike CO_2 reactivity, the response of CBF, after established hypoxemia, is a longer process, taking about 6 minutes (208, 209).

Results from animal studies, on the effects of hypoxia, show that CBF does not change until systemic PaO_2 is less than 50 mmHg. Below this value, there is a vasodilatory response and a subsequent increase in CBF (152, 153). Studies in

humans, also demonstrate an increase in CBF with moderate hypoxia (91, 102). A PaO_2 value of less than 58mmHg (7.9kPa) or SaO_2 less than 90% is associated with an increase in middle cerebral artery (MCA) blood flow velocity and decreased cerebral vascular resistance, as measured with TCD (91). It is therefore important to note, particularly in TBI, that the change in CBF with hypoxia is not related to alteration in CPP, but rather to changes in local tissue oxygen content (155).

Carbon dioxide (CO_2) vasoreactivity

The cerebral circulation is exquisitely sensitive to changes in $PaCO_2$, a mechanism commonly referred to as CO_2 vasoreactivity. CBF increases linearly by 2-4 % per mmHg increase in $PaCO_2$, within the range of 25-75 mmHg (210). Changes in CBF occur within seconds of altering $PaCO_2$, with complete equilibration usually occurring within 2 minutes. Hypercarbia results in vasodilatation and increased CBF, whereas hypocarbia results in vasoconstriction and decreased CBF. CO_2 vasoreactivity is usually preserved after severe head injury. It may however be weaker in the early stages after injury, but usually returns to the normal 2-4% change per mmHg CO_2 by 24 hours after injury (214-217). Regional CO_2 reactivity differs from global CO_2 reactivity, as demonstrated by Marion and colleagues (218). Severe impairment of CO_2 vasoreactivity usually reflects an increased severity of injury and a poorer prognosis (215,216).

Variation in CO_2 leads to changes in vessel caliber followed by a passive change in CBF. These vessels respond to changes in the pH of the perivascular spaces secondary to alterations in $PaCO_2$. CO_2 crosses the blood brain barrier freely, and is therefore able to change the pH in the perivascular spaces. However, if the new $PaCO_2$ level remains constant over the next 24 hours, the pH in the blood and the perivascular space as well as the diameter of the cerebral blood vessels, returns to baseline (213). The constant supply of substrate to the brain is maintained at the level set by metabolism ($CMRO_2$). Therefore, with CO_2 reactivity, changes in CBF are compensated for by changes in $AVDO_2$. CBF vasoreactivity in anesthetized healthy

children is higher than in adults, according to data derived from studies using propofol and volatile anesthetics (211,212).

Temperature

The primary temperature regulation centre in humans is the anterior preoptic region in the hypothalamus. This centre is responsible for maintaining body temperature at 36.8 – 37.2 ^{o} C (219). The brain temperature itself, is dependent on several factors, including: *cerebral metabolism, CBF (local, global), and the external environment (radiation, conduction and convection).* The temperature of incoming arterial blood is considered to be the main determinant of brain temperature, particularly for the deep brain structures (220). The effect of extracranial temperature on the more superficial brain structures is unclear. The thermoregulatory response of the human brain to environmental changes, reflects the severity and localization of the cell damage (226). Brain temperature is largely assumed to follow core temperature when cooling is used. This remains an important issue, as numerous attempts have been made to use hypothermia for the treatment of stroke, TBI and multiple sclerosis (221-225).

Acid/base (pH) regulation

The regulation of pH is fundamental to the viability of cells. In this respect, the cells in the central nervous system (CNS), do not differ from those found in other tissues, and the mechanisms responsible for long-term control of hydrogen ions are similar. The cellular diversity of the CNS, however, is unique, and there are a number of different acid transport mechanisms encountered in the subtypes of neurons and glial cells within the CNS. The acid-base physiology of the CNS is also distinguished by the occurrence of rapid changes in H^{+} ions that arise from electrical activity. These changes take place over time periods ranging from milliseconds to minutes, involve neurons and glia, and occur in both the intracellular and extracellular compartments. The mechanisms that generate and regulate these pH changes are of

considerable neurobiological significance, as they may have a modulatory role in membrane potential and excitability (227). These mechanisms include Na^+/H^+ exchange, Na^+-dependent bicarbonate (HCO_3) transport and a passive Cl^-/HCO_3 exchanger.

pH microelectrode studies have shown that brain interstitial fluid is slightly more acidic than blood, with a pH of ± 7.3 (229). These studies also show that the low pH of the interstitial fluid is entirely due to elevation in tissue pCO_2. The high concentration of CO_2 in post-mortem brain specimens is likely due to its generation through aerobic metabolism, and poor clearance, owing to a lack of blood flow. In vivo, CO_2 is usually cleared by blood flow, which prevents accumulation of CO_2. With a physiological rise in perfusion, due to elevated neural activity, increased clearance of CO_2 and local increases in brain pH could, in principle, occur (228).

CHAPTER 3: THE PATHOPHYSIOLOGY OF HYPOXIA AND ISCHEMIA

Despite the high metabolic demands of the brain and the requirement for continuous supply of oxygen and glucose, there is no capacity within the brain for storage of oxygen, and only a limited reserve of high energy phosphate compounds and carbohydrate reserves. These reserves are only adequate to supply brain tissue for a very short period, less than a minute (162, 163), without adequate perfusion, making loss of perfusion a major cause of acute brain injury. The terminology and subsequent definition of pathological conditions contributing to abnormalities of CBF, cerebral oxygenation and cerebral metabolism, have been the subject of much discordance and debate. Terms like 'oligemic cerebral hypoxia', 'metabolic crisis', 'post traumatic cerebral ischemia' or 'cerebral hypoxia', have all been used in the description of the pathophysiology following injury to the brain (142).

Cerebral hypoxia may be described as a reduction in cerebral tissue PO_2 levels to a level insufficient to maintain cellular function and structure. Hypoxia, is usually associated with inadequate ventilation. A decrease in the systemic PaO_2 to below 35mmHg triggers the onset of anaerobic metabolism, which is associated with an increase in cerebral glucose consumption, so called hyperglycolysis, and an increase in lactate production (164). Apart from the direct effects of systemic hypoxia, prolonged systemic hypoxia also often leads to a gradual decrease in blood pressure and subsequently reduced cerebral perfusion pressure, a decrease in extracellular pH and ultimately, an increase in the lactate/pyruvate ratio.

Cerebral ischemia implies a reduction of CBF to values that cannot sustain normal cerebral metabolism and function or maintain tissue structure. The distinction between hypoxia and ischemia is not always that obvious, as they can both lead to cerebral oxygen deprivation and cell death. Ischemia differs from hypoxia in that it involves a reduction in blood supply as well as an interruption in the supply of

oxygen. There is therefore an accumulation of metabolic products in ischemia, which includes CO_2, lactic acid and ammonia.

The degree to which brain tissue is damaged depends on the duration and severity of ischemia. In the absence of an adequate oxygen supply, the tissue can obtain energy only by utilising energy-rich phosphate reserves, like those obtained from adenosine triphosphate (ATP) and adenosine diphosphate (ADP). When severe or prolonged, however, ischemia rapidly leads to cell death in the affected area of the brain. The severity of the injury depends on the extent of the ischemia and the location of the involved brain. These ischemic cerebral lesions in TBI ranging from small foci of neuronal necrosis to frank infarction, are relatively common in fatal blunt head injury (20, 22). Even brief periods of transient ischemia may result in selective neuronal necrosis that only manifests after hours, days, weeks or months (23-26).

When ischemia is incomplete, there is a reduction in CBF, but some residual 'trickle' flow persists. To compensate, the brain increases the fraction of the oxygen content of arterial blood extracted, known as the oxygen extraction factor (OEF). However, this is a limited compensatory mechanism. Residual perfusion of the tissue may still permit an ongoing supply of glucose to the tissue, which ultimately leads to an increase in lactate production and cerebral acidosis. The degree of cerebral acidosis in incomplete ischemia, can therefore be more profound than in total ischemia.

An analysis of the tissue metabolite levels, viz. ATP, ADP, lactate and pyruvate, provides an indication of the balance between mitochondrial energy production and usage. This may in turn provide an adequate method of evaluating the degree of circulatory restoration. Transient ischemia usually occurs in three phases : 1) the ischemic insult, 2) a period of complete or partial recovery of function and metabolism, and 3) a period in which secondary damage becomes manifest. The importance of identifying these phases is that the second phase may represent a window of opportunity to intervene (27).

The thresholds for CBF in cerebral ischemia have been described by various authors over the years (28-34, 125). Reduction of cortical blood flow to levels of

approximately 20ml/100g/min often may be tolerated without any significant functional consequences, however, loss of consciousness and electroencephalographic slowing may occur. If CBF decreases below 18ml/100g/min, ionic homeostasis becomes jeopardized and neurons convert to anaerobic metabolism (157, 158, 159). At a CBF of 10ml/100g/min, membrane integrity is lost and massive calcium influx ensues, leading to irreversible damage. Tissue infarction is also time-dependent, as discussed earlier, and will occur with a CBF of 5ml/100g/min lasting for more than approximately 30minutes, at a CBF of 10ml/100g/min for more than 3 hours, 15ml/100g/min for more than 3.5 hours, or 18ml/100g/min for more than 4 hours (160, 161). These studies were done mostly on adult stroke models. The generalizability of these data to TBI, and children in particular, is limited by the complexity of TBI and the differences between adult and pediatric cerebral physiology.

Classification of cerebral ischemia.

Ischemia may be global or focal (35-38). *Global ischemia* may be brief, caused by global insults like cardiac arrest, which affect all brain areas similarly. Recovery from such insults have been reported only after ischemic periods of 15 minutes or less (at temperatures of 37-38 ^{0}C) (84). *Focal ischemia* is a different entity to global ischemia in many ways (35, 36, 39, 40). It may occur in cerebrovascular disease, subarachnoid hemorrhage (SAH) and TBI. The ischemia affects primarily the territory supplied by the affected vessel, while surrounding tissue is variably affected. Therefore the severity of the ischemia varies from dense ischemia in the area supplied by the occluded artery (the focus, or the core) and less dense ischemia in the surrounding areas that receive blood from collateral vessels (the penumbra) (46-50).

Focal ischemia caused by MCA occlusion, differs from global ischemia because the reduction in CBF is less severe, but usually more sustained. And so there are significant differences in cerebral energy states during global ischemia and following MCA occlusion (42-45). Induced transient MCA occlusion for 15 to 18 minutes, in monkeys, showed no damage, with some tolerating occlusion for up to 60 minutes

(41). Focal tissue areas are usually irreversibly damaged, as their blood supply is usually too feeble to sustain the cells beyond the initial 15 to 30 minutes of ischemia. In contrast though, even when the perifocal areas are at risk, they remain viable for longer periods. With a good collateral supply, viability may be preserved for a few hours (46). The size of the infarcted tissue usually grows in size though, as the perifocal tissue is recruited in the infarction process. As this recruitment period takes some time, it may provide a "window" of therapeutic opportunity during which perifocal tissue could be salvaged, by either pharmacological interventions or reperfusion.

Mechanisms of ischemic brain damage: molecular changes and cellular death.

Understanding of the complex mechanisms and interactions involved in the pathophysiology of ischemic brain damage, has in recent years increased considerably. Mitochondria within the brain are extremely sensitive to ischemic insults. The initial response to an ischemic insult is a substantial impairment in the electron transport chain, which may be followed at a later stage by reductions in the levels of ATP and phosphocreatine (PCr). The role of mitochondrial dysfunction in neural energy failure and cell death has been highlighted in both traumatic and ischemic brain injury (165, 166, 167). While cell death was traditionally thought to occur either by necrosis or apoptosis, recent arguments suggest that these are not separate and distinct events, but rather lie on a continuum (168, 169). Recent evidence suggests that these two systems are linked by the regulation of calcium (Ca^{2+}) within the cell, and even more importantly, by the mitochondria (170). Decrements in the vasodilatory response to nitric oxide (NO), cyclic guanosine monophosphate, cyclic adenosine monophosphate, and prostanoids were all reported as possible mechanisms underlying posttraumatic hypoperfusion and subsequent ischemia (264-266). In studies, done in pigs and rats, release of the vasoconstrictor, endothelin-1, post injury, and loss of endothelial NO production were postulated as possible mediators of the post-traumatic ischemia (267, 268). Loss of vasodilators and elaboration of vasoconstrictors may therefore have a significant

role in facilitating ischemic injury. It is, however, not clear whether the immature brain is more or less prone than the adult brain to develop hypoperfusion after TBI (272).

The two major hypotheses to explain cell death, are the calcium hypotheses and the excitotoxic hypothesis. The *calcium hypothesis* proposes that massive influx of calcium into cells, due to disruption of the plasmalemmal Ca^{2+}-ATPase (controlling efflux), leads to cell death by catalyzing the breakdown of structural components of the cell. These are mainly membrane lipids, cytoskeletal proteins and most importantly mitochondria (57, 58, 59). The *excitotoxic hypothesis*, suggests that excitatory amino acids (EAA) eg. glutamate, related toxicity leads to neuronal cell death in tissue (61, 62, 64). Although glutamate is the most abundant neurotransmitter in the brain, exposure to toxic levels produces neuronal injury in two phases. Minutes after exposure, sodium-dependent neuronal swelling occurs, resulting in "osmolytic damage". This is followed by delayed damage due to calcium influx (61-65). These processes initiate cell death by setting in motion various reactions viz. enhanced lipolysis, altered phosphorylation of proteins, enhanced production of reactive oxygen and nitrogen species, dissolution of the cytoskeleton and fragmentation of DNA.

One of the major problems in understanding ischemic thresholds in TBI is that the quoted thresholds for CBF in cerebral ischemia, are based on studies done largely in adult stroke models. These thresholds may not be appropriate for ischemia in TBI as there are fundamental differences in the pathophysiology of the two conditions. The most important of these is the uncertainty regarding the metabolic activity of the brain and whether or not the altered CBF is coupled to an underlying metabolic depression. If there is uncoupling of metabolism, a normal CBF may actually be inadequate for areas of increased metabolism Increases in metabolic demands early after TBI related to uptake of glutamate, demonstrated by increased brain and CSF lactate levels, have been reported (269, 270) This difficulty in equating an absolute CBF value with ischemia in TBI, has led to the need for assessing other relevant parameters, which include OEF, $CMRO_2$, $SjvO_2$, CvO_2, lacate /pyruvate ratio and

$AVDO_2$. This need has stimulated numerous investigators to employ a variety of modalities in order to best demonstrate the burden of ischemia in TBI. These modalities will be discussed in the following chapter.

CHAPTER 4: Methods of monitoring for cerebral ischemia

Detecting cerebral ischemia, or a surrogate marker of ischemia, can be attempted by using several different monitoring modalities. These may be either invasive or non-invasive, allowing either a continuous or 'snapshot' recording of local, regional or global brain functional parameters. They may directly measure tissue perfusion, oxygenation or metabolism or measure surrogate markers of the adequacy of oxygenation, like CBF, CBV, CPP and ICP. **Invasive methods** include, brain tissue oxygen tension monitoring ($PbtO_2$), jugular venous saturation ($SjvO_2$), cerebral microdialysis (MD) and CBF (thermal perfusion) monitoring, the key features of these monitoring techniques are summarized in table 1. **Non invasive methods** include imaging techniques like combined positron emission tomography (PET), xenon enhanced computed tomography (Xe-CT), perfusion computed tomography (perfusion CT), single photon emission computed tomography (SPECT), various MRI sequences and techniques, as well as other bedside or portable modalities, such as near infrared spectroscopy (NIRS), transcranial Doppler (TCD), electroencephalography (EEG) and somatosensory evoked potentials (SSEP), the key features of these monitoring techniques are summarized in table 2.

Invasive methods

Brain tissue oxygen monitoring ($PbtO_2$)

Direct $PbtO_2$ monitors are probably the most frequently used technique for measuring regional brain oxygenation, due to their relative ease of use (76). The most commonly used device is also the one about which there is the largest body of evidence in the literature, i.e Licox system (Integra Neurosciences, Plainsboro, NJ, USA). Other $PbtO_2$ devices include the Neurotrend (Codman, no longer commercially available) and Neurovent-PTO (Raumedic, ICP and $PbtO_2$).

$PbtO_2$ is measured using a fine probe which is usually inserted into white matter parenchyma. The readings from the sampling area (about $14mm^2$) are determined by the amount of oxygen diffusing across a thin membrane, which covers the 2 electrodes of a polargraphic cell (66). The cell used is a Clark-type electrode, which uses the electrochemical properties of noble metals to measure the oxygen content of tissue. Therefore the greater the oxygen partial pressure, the more oxygen diffuses through the membrane. $PbtO_2$ readings are not a direct measurement of total oxygen delivery or cerebral oxygen metabolism. Rather, measurements of $PbtO_2$ were shown to represent the product of CBF and arteriovenous oxygen tension difference, suggesting a strong association between $PbtO_2$ and diffusion of dissolved plasma oxygen across the blood-brain barrier (158).

The monitor provides a measure of $PbtO_2$ in units of tension (mmHg). The readings obtained from these monitors are continuous, and have been shown to be reliable in vitro, with minimal drift over time (67-72). These readings are usually stable about 2 hours after insertion, local tissue damage is minimal and complications are rare (68, 69, 73, 74). The ease of use and potential benefit of continuous brain oxygenation monitoring, coupled with the ability to measure the response to interventions, render this method particularly appealing and increasingly popular in the neurointensive care unit (NICU) (75, 76, 77). $PbtO_2$ guided management may also assist in deciding the optimal CPP for individual patients, so avoiding the potentially harmful effects of raising CPP in all TBI patients (207). However, the major limitations are the very focal measure of oxygen tension produced and the fact that several other factors influence $PbtO_2$ readings, eg. inspired fraction of oxygen, hemoglobin level, arterial carbon dioxide level, cerebral oedema and anatomical location of the catheter tip. It is, therefore, not simply an ischemia monitor, although ischemia may be one of the important contributors to reduced $PbtO_2$.

Jugular venous saturation ($SjvO_2$)

$SjvO_2$ was, for a long time, the most widely used method of monitoring cerebral oxygenation (78, 85, 86). $SjvO_2$ measurements are obtained by placing a fiberoptic

oxygen-sensing catheter into the jugular bulb for continuous recording or intermittent sampling (78). The readings obtained are more indicative of global cerebral oxygenation or at least hemispheral oxygenation, which has been considered by some to be an advantage, when compared directly to $PbtO_2$ (85). $SjvO_2$ monitoring offers continuous and real-time display, but is more susceptible to artifacts and reduced time monitoring (80). It is more prone to technical problems and vigilance is required to obtain reliable data. Frequent recalibration and special attention to matters such as poor light intensity, head movements, spontaneous waves, or sudden changes are required to obtain adequate "time of good data quality" (81-83). The choice of which side to use has also been discussed, but most commonly the dominant hemisphere is chosen (84), although some may choose the more injured hemisphere or bilateral monitoring. Another potential shortcoming of $SjvO_2$ monitoring, as demonstrated by Coles et al in 2004 (11), is the limited ability to provide reliable information about focal ischemia. This limitation of $SjvO_2$, especially when compared to $PbtO_2$ monitoring, has been a large factor in $PbtO_2$ monitoring being used as the preferred method of monitoring cerebral oxygenation, especially in recent years (79,91). Various factors influence $SjvO_2$, the two most important of which are CBF and cerebral metabolic rate of oxygen consumption ($CMRO_2$). Therefore an increase in CBF or a decrease in $CMRO_2$ may lead to an increase in $SjvO_2$. Conversely, a decrease in CBF or increased $CMRO_2$ leads to a decrease in $SjvO_2$. The reference range for 'normal' values for $SjvO_2$ lies between 50% and 75% (86). A decrease in $SjvO_2$ to below 50% for at least 10 minutes has been suggested as a critical threshold (87), however this is debated. Desaturation episodes correlate with a poorer outcome in patients who have sustained TBI, particularly when these episodes occur more than once during the patient's course of treatment (89, 94). The association of abnormal $SjvO_2$ values with poor outcome has been demonstrated by numerous authors (87, 88, 89). However, it is not only low $SjvO_2$ values which are negatively prognostic, as increased $SjvO_2$ values have also been associated with poorer outcome (87). The association with low $SjvO_2$, however, seems to be stronger (88). Ideally, other cerebral parameters should be monitored concurrently to assist in the interpretation of $SjvO_2$ changes. An increase in ICP, decrease in CBF, or a

decrease in peripheral arterial blood saturation (SaO_2), all improve the understanding of synchronous $SjvO_2$ changes (95). In pediatric TBI, there is limited data correlating $SjvO_2$ and outcome. The available data, however does suggest an association between more than one episode of $SjvO_2$ readings below 50% and poorer outcome (92).

Microdialysis (MD)

Cerebral microdialysis (MD) was first introduced in the 1970's by Delgado and Ungerstadt (172, 173). The original idea was to implant an artificial capillary into brain tissue to facilitate sampling of interstitial fluid for analysis of neurochemical markers. However, it was only introduced as an intracerebral sampling method for clinical neurosurgery in 1990 (174) and has been embraced largely as a research tool to measure neurochemistry in TBI and other neurological conditions. The basic MD system consists of a catheter for tissue implantation and a perfusion pump. The diameter of the catheter is approximately 1mm. It consists of a double lumen and has a semi-permeable membrane attached at the tip. The dialysate used in MD, is a fluid that is isotonic to the interstitial fluid (ISF). This facilitates mass transport of molecules across the membrane which are driven by diffusion across a concentration gradient. Therefore, at a constant perfusion rate, the concentration of a certain molecule in the dialysate will be proportional to the concentration in the perfusate/ISF. This ratio is referred to as the relative recovery. The technique can therefore enable frequent sampling and monitoring of chemical changes in the ISF with a maximal time resolution of 1-20 minutes. Prior to the introduction of MD, neurochemistry of the brain was primarily evaluated indirectly via samples of cerebrospinal fluid (CSF). The greatest advantage offered by MD, was that it provided a semi-continuous method for analysis of the chemical constituents of the extracellular space, and thus also brought the hope for new insights into the neurochemistry of TBI and the possibility of neurochemical monitoring in neurointensive care management. The most notable neurochemical markers in TBI are aimed at markers of metabolism, including, glucose, lactate, pyruvate,

lactate/pyruvate ratio, lactate/glucose ratio and pH. While MD is one of very few methods for neurochemical measurements in the interstitial compartment of the human brain, it has several limitations restricting its use as a clinical monitoring tool in TBI patients. These include, concerns about the focality of monitoring, complicated issues related to quantification of data, implantation strategies, appropriate choice of markers, quality assurance, and the cost and infrastucture required. The role of MD, currently, remains as a research tool and its use has been restricted to a few institutions.

Cerebral blood flow (CBF) via thermal perfusion monitoring

Direct CBF/perfusion monitoring in TBI, has only been reported on by a few investigators (60,180,181,182). The technology originated from work done at the Massachusettes Institute of Technology (MIT), by Dr. H.F. Bowman. Perfusion monitoring aids in the assessment of tissue as well the reaction of tissue to induced physiological changes. It therefore, potentially facilitates rapid detection of change in perfusion level and allows recording of long-term perfusion levels to monitor changes over a course of treatment. The probe may be inserted via a cranial bolt, and is usually inserted to a depth of 2cm into the least injured hemisphere (158). The probe contains two thermistors embedded at the tip of a polyurethane catheter. The distal (heating) thermistor is heated to a small increment (approximately 2.5^{o}C) above the tissue temperature baseline, while the proximal (sensing) thermistor tracks the tissue baseline temperature. The power dissipated by the heated thermistor provides a measure of the tissue's ability to carry heat by thermal conduction in the tissue and thermal convection in blood. The monitor measures tissue perfusion by determining the conductive properties of the tissue, and produces a real-time simultaneous measure of perfusion and temperature at the site. The accuracy of perfusion measurement is highly dependent on proper and stable probe placement, as the monitor is sensitive to motion artifact. The Bowman Perfusion Monitor (Hemedex, Inc, Cambridge, MA, USA), is the commercially available unit.

Table 1. Invasive Methods of monitoring

MONITORING TECHNIQUE	ADVANTAGES	DISADVANTAGES	QUANTITATIVE	QUALITATIVE	REFERENCES
Brain tissue oxygen tension monitoring (PbtO2)	1. Provides continuous real- time information. 2. Relatively safe monitoring modality. 3. Useful as part of multi-modality monitoring, to interpret abnormalities in other parameters. 4. Catheters have minimal drift over time.	1. Provides a measure of only local cerebral oxygenation, so has poor spatial resolution. 2.Readings are influenced by various factors and it is not an ischemia monitor per sè, with relatively poor specificity.		*	Kiening et al-67, Dings et al-68, Zauner et al-69, Maas et al-71, Van den Brink et al-73, Figaji et al-76, Rosenthal et al-158, Stieffel et al-207
Jugular venous saturation monitoring ($SjvO_2$)	1. Measures global oxygenation. 2. Provides continuous real- time information. 3. May be used in conjunction with focal monitors to provide more comprehensive information.	1. Prone to many technical problems. 2. Requires frequent recalibration. 3.Provides limited information on focal ischemia. 4. Readings are influenced by a variety of factors, so has poor specificty.		*	Valadka et al- 79, Sheinberg et al-80, Robertson et al-81, Stocchetti et al-82, MacMillan et al-86, 88, Gopinath et al-89
Microdialysis (MD)	1. Provides neurochemical measurements in the interstitial compartment. 2. Used in conjunction with other modalities eg. PET, to provide a better	1. Used mainly in research capacity. 2. Difficulties in quantification and bedside presentation of MD data. 3. Use of the technology is	*		Delgado et al-172, Ungerstedt et al-173, Hillered et al-174

	understanding of the pathophysiology of TBI. 3. Allows frequent sampling and monitoring of chemical changes in the interstitial fluid.	considered labour intensive. 4.It is a focal monitor. 4. Does'nt provide real-time data. 5. Requires significant cost and infrastructure.			
CBF/Perfusion monitoring	1. Useful as part of multimodality monitoring in head injury.	1.Requires frequent calibration. 2. Limited reports on its use. 3. Provides information on local CBF, so has poor spatial resolution. 4. Accuracy is dependent on proper placement of the probe.		*	Jaeger et al-60, Vajkoczy et al-180, Clausen et al-181, Hemphill et al-182

Non Invasive methods

Positron emission tomography (PET) scan.

The principle of PET imaging is based on the emission of a positron from the active isotope within the tissue. The emitted positron, a low energy particle, travels only a few millimetres before combining with an electron in the tissue. This collision results in annihilation of the two particles with the emission of two high energy gamma rays. These gamma rays are emitted in nearly exactly opposite directions, and are detected by a pair of external circumferential detectors, situated 180 degrees from

each other. The localizing capability and striking images provided by PET, rely on these detectors picking up simultaneous gamma ray signals. These images represent the quantitative distribution of a radiotracer of specific biologic importance. By comparing the clearance of the positron emitting isotope with the location of the annihilation event, this modality is able to provide critical physiological and biochemical measurements (282). Oxygen-15 positron emission tomography (O^2 PET) imaging has been used to determine cerebral blood flow (CBF), cerebral blood volume (CBV), cerebral metabolic rate of oxygen consumption ($CMRO_2$) and oxygen extraction fraction (OEF). Some studies have suggested that this imaging modality may provide a robust and specific definition of true ischemia (12). PET scanning has also been used in conjunction with other monitoring tools and imaging modalities, as a 'gold standard' to validate and refine bedside monitors of cerebrovascular physiology. It has also been used to study the impact and adequacy of therapeutic interventions aimed at treating and preventing cerebral ischemia. The relevance of using PET scanning to answer questions related to the pathophysiology of TBI, as well as assessments of the feasibility and safety of this modality have been validated by early seminal papers (109, 110). An acceptable definition of regional cerebral ischemia depends on the demonstration that CBF is inadequate for oxygen demands. This suggests that local OEF should be increased or $CMRO_2$ decreased in these regions. The triple oxygen study PET is the most commonly used protocol for PET scanning, providing information on $CMRO_2$ and OEF. PET also has other capacities, beyond its application in demonstrating cerebral ischemia, including the additional information derived from fluorodeoxyglucose (FDG), fluoro-omisonidazole and PK1195, as markers of abnormal substrate handling in ischemia, tissue hypoxia and cerebral inflammation, respectively (112, 113). However, there are several distinct disadvantages of PET scanning. These include, most notably, the need to transfer patients out of a critical care environment (requiring stable patients), the need to administer radiation, relatively poor spatial resolution at 2-4 cm^3 and the lack of 'within-modality correlations' (compared with magnetic resonance imaging). Most importantly, although PET allows detailed information to be derived, it is limited to a 'snapshot' of the brain at one point in time, a significant limitation in practical

neurocritical care, given the temporal heterogeneity and dynamic nature of TBI. Finally, very few specialized centres have access to PET scanners due to the expense and infrastructure required.

Xenon-enhanced CT scanning

In this imaging modality, non-radioactive xenon gas is inhaled and the temporal changes in radiographic enhancement produced by the inhalation, are measured by sequential computed tomography. The importance of techniques designed for measuring CBF, both regional and global, have been well established by various studies demonstrating the importance of this relationship over the years (114, 115). The introduction of rapid, sequential transmission CT provides a method of monitoring changing tracer concentrations over time with a high degree of anatomical specificity (116, 117). The local CBF in extremely small tissue volumes is derived from measurements of time dependent concentrations of nonradioactive xenon gas. These methods employ sequential CT scanning of one or more brain slices during the inhalation of xenon/oxygen mixtures in order to detect the build-up or wash out of xenon in tissue. Xenon is a freely diffusible tracer which readily crosses the blood brain barrier, its time dependent concentration in tissue can therefore serve as an indication of tissue perfusion. Xenon tends to yield measurable image enhancement even when it is inhaled in relatively low concentrations. This is largely due to the relatively high atomic number of xenon, i.e. 54. Local CBF is calculated using the Fick principle, which states that tissue uptake of an indicator is equal to the amount supplied by the arterial blood less the amount drained by the venous blood (118). Briefly, the actual procedure involves the acquisition of three or more images preceeding, during and/or after a period of four to six minutes of xenon/oxygen inhalation. During this period xenon concentrations in the inspired and expired gas are monitored continuously and end–tidal xenon levels are assumed to be proportional to time dependent xenon concentrations in arterial blood (119). The result is then used in conjunction with time dependent xenon concentrations in tissue to derive a partition coefficient and local CBF for each specific tissue of

interest. Most early studies reporting the results of Xe-CT were done on lightly anesthesized baboons, with normal and infarcted brains (119). Xenon concentration from 20-80% were used in these studies and the results indicate that while signal-to-noise improves with increased concentration, time dependent patterns when xenon concentrations fall below 40 percent are similar to those observed with higher xenon concentrations. Using this methodology, flow can be consistently characterized in tissue with fast, slow and extremely slow flows (i.e. infarcted tissue).

However, there are also significant shortcomings associated with Xe-CT, these include: the high dose of radiation due to repeated scans at the same level, patient motion during procedure, the side effects of xenon itself i.e. possible increase in ICP, EEG alterations and a slow decrease in local CBF and the fact that xenon is no longer FDA approved, restricting its use (in the USA). Like PET it has limited temporal resolution in that it provides a snapshot of the brain at one point in time. Unlike PET though, it does not allow the interpretation of CBF relative to the underlying metabolic activity of the brain.

Single photon emission computed tomography (SPECT)

SPECT is a functional neuroimaging technique which provides another non-invasive method for studying both physiological and pathophysiological changes in the human brain. SPECT is mostly used to demonstrate a patient's pathological status when neurological symptoms cannot be explained by structural neuroimaging findings alone. It is sensitive in detecting impairment in regional cerebral function when CT or MRI shows only non-specific findings e.g. cerebral atrophy. The defects noted on SPECT are also frequently larger than those noted on CT, largely because SPECT imaging represents a combination of a central zone of infarction, surrounded by a penumbra zone of ischemia, as ipsilateral cortical diaschisis may also contribute to the size of the defect (183). SPECT is also more sensitive than CT in the early (within 24 hours) detection of acute ischemia (183, 184). The high sensitivity in detecting functional impairment, however, is counterbalanced by poor specificity as the same SPECT pattern may be encountered in different pathologies. The

association between CBF, metabolism and neuronal activity is the basis for the use of brain perfusion SPECT. Interpretation of these images, therefore, requires a detailed knowledge of both the patient's symptoms and the functional areas of the brain likely to be involved. This can also be used to sequentially track changes in regional cerebral perfusion over time (185). The usage of brain perfusion SPECT as a clinical research tool has been favoured in the investigation of sensory, motor and cognitive studies (neuroactivation studies) as well as in the assessment of the effect of drugs on the central nervous system (pharmacologic challenge) (186).

The appropriate selection of a radiopharmaceutical agent is important, as both the pharmacokinetics of the compound and physical characteristics of the isotopes influence the technical aspects of the investigation. The common biological properties of these radiopharmaceuticals include: the ability to cross the blood-brain barrier, distribution in the brain proportional to blood flow and retention in the brain with a fixed regional distribution for a sufficient time to permit image acquisition (20-30 min). To quantify regional CBF (rCBF) by means of brain perfusion SPECT, the diffusible gas ^{133}Xe, was previously considered the radiopharmaceutical of choice (187). Due to several limitations, including a rapid clearance time, a low gamma ray energy (causes poor quality images) and requiring active patient cooperation, however, it has fallen out of favour. Other brain SPECT tracers such as ^{123}I-labeled amines {^{123}I-isopropyliodoamphetamine (^{123}I-IMP)} and technetium-labeled (^{99m}Tc) compounds {hexamethamethylpropylenaneamine oxime (^{99m}Tc-HMPAO) and ethylcysteinate dimer (^{99m}Tc-ECD)}, offer higher resolution SPECT images after intravenous administration. These tracers seem to have found more acceptance even though they allow only quantitative estimations through their tracer uptake ratios. Absolute rCBF measurement using SPECT has not been fully implemented and the region of interest (ROI) analysis of rCBF has become the preferred method of quantification (183).

In the initial assessment of patients with mild and moderate TBI, SPECT was found to be more sensitive in detecting brain lesions than CT (187, 188). It is also particularly useful in patients with persistent neurobehavioural abnormalities after

mild degrees of trauma when the CT and MRI studies are normal. While SPECT imaging may demonstrate areas of hypoperfusion in TBI patients who have abnormal neuropsychological tests (188), the pathophysiology and prognostic significance of these findings remain unclear.

Perfusion CT

Perfusion CT is a technique that provides rapid qualitative and quantitative evaluation of cerebral perfusion. The main principle of perfusion imaging revolves around the analysis of plain and contrast-enhanced CT scans obtained at different times. The technique is based on the central volume principle, which relates CBF, CBV and mean transit time (MTT), using the equation: CBF = CBV/MTT. Perfusion studies therefore generate maps of CBF, CBV and MTT by monitoring the passage of an iodinated contrast agent through the cerebral vasculature. The linear relationship between concentration and attenuation, therefore leads to an increase in attenuation proportional to the amount of contrast in the region. Arterial and venous regions of interest (ROI) are generated, based on the time – concentration curves produced by these contrast agents. Complex mathematical calculations are then used for ' deconvolution ' of these enhancement curves, in order to generate a MTT. CBV is then calculated as the area under the curve, and using the central volume equation the CBF can then be calculated (189,190).

The dose of radiation required for perfusion CT is 2.0-3.4 mSv, which is only slightly higher than that required for a routine CT head (1.5-2.5 mSv). This dose equivalent is less than the dose equivalent obtained with PET or SPECT and is comparable to that of a single level xenon CT examination (191,192). The main clinical indications for the use of perfusion CT are: acute stroke, perfusion assessment in the acute phase of TBI, assessment of cerebrovascular reserve, temporary balloon occlusion tests, vasospasm in SAH and the measurement of microvascular permeability in tumours (193).

In the acute phase of mild TBI, perfusion CT has detected abnormalities of CBF and CBV in cases where the admission non-contrast CT scan was normal (194). The

applicability and prognostic significance of this investigation in acute TBI lies in its ability to better delineate the ambiguous nature of hypodense areas on non-contrast CT that may represent either necrotic or viable tissue (195). The depiction of brain perfusion abnormalities and their regional heterogeneity early on in pediatric and adult TBI, could significantly impact the diagnosis, aggressiveness of treatment and may also offer valuable prognostic information (196,197).

MRI sequences

Magnetic resonance imaging (MRI) has an important role to play in assessing brain injury in children. Unfortunately, most MR sequences are designed for imaging the adult brain and need to be adapted to obtain high quality images of the immature brain with its high water content. Conventional MRI sequences provide excellent and detailed information about the pattern of lesions following pediatric and perinatal brain injury. Specific advanced MRI techniques may provide additional relevant and prognostic information, when evaluating ischemic brain injury. These techniques include diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), perfusion–weighted imaging (PWI) and magnetic resonance angiography (MRA).

Diffusion-weighted imaging (DWI) is a measure of the random motion of water within tissue. The apparent diffusion coefficient (ADC) provides a means of quantifying this random motion or diffusivity. In children, DWI has been used mostly to assess tissue injury in neonates with perinatal stroke (230). The evolution of the diffusion abnormality in perinatal ischemic brain injury appears to be similar that seen in adults (231). In order to improve the sensitivity of detecting abnormal tissue, a fluid-attenuated DWI technique is often used, particularly where the partial volume effect of CSF may make ADC values inaccurate (232). Reduced ADC values within the brainstem of neonates with perinatal brain injury have been reported, but it is still unclear whether ADC values provide a more sensitive measure of later outcome following perinatal stroke (233,234). To maximise the predictive abilities of the diffusion techniques to correctly identify ischemic tissue, it is essential to

consider the timing of the injury, the age of the patient and the conventional imaging appearances, together with the DWI characteristics and ADC measurement.

Diffusion tensor imaging (DTI) is a diffusion-weighted technique which allows the measurement of the directional diffusivity of water or anisotropy as either regional (RA) or fractional anisotropy (FA). Anisotropy has been shown to be useful for the timing of an injury in adults, demonstrating no hyperacute changes within 6 hours of symptoms (235). Anisotropy increases with age because myelination results in decreased radial diffusivity perpendicular to white-matter tracts, and is variably deranged following acute focal infarction (236). A combination of ADC and FA values derived from DTI combined with visual analysis of conventional imaging currently offers the best approach for identifying abnormal tissue and estimating the timing of the insult (237).

Perfusion-weighted imaging (PWI) most often is used to assess tissue viability in adult stroke, usually in conjunction with DWI. Contrast enhanced PWI techniques are generally preferred to non-contrast techniques like arterial spin labelling, due to the poor signal to noise ratios (SNR) of the latter. PWI may have many applications in studies of the neonatal brain but there are few studies published (238). The main difficulties with PWI studies in the immature brain are motion artifact, difficulties in obtaining data of the normal brain, and problems with quantification. Perfusion of the neonatal brain shows regional heterogeneity. Neonates with extensive white matter infarction may show both relative under and over-perfusion of this tissue. Although PWI has already allowed insights into the response of the immature brain to hypoxic-ischemic injury (237), it remains a challenging technique in the very young because the pathologies and reponses of the brain are different.

Magnetic resonance angiography (MRA) is a well established non-invasive technique for imaging the intracranial vasculature at 1.5 Tesla and lower magnetic field strengths, mostly in adults. Neonatal imaging, using the same technique to study vessel anatomy and blood flow, has been relatively underutilized (237). Angiography of the circle of Willis and carotid arteries and venograms of the dural sinuses are useful for describing anatomic variations and determining whether these

predispose to brain inury in a given clinical situation. Compared to adult vessels, neonatal vessels are smaller, with lower blood flow velocities, making MRA of the immature brain a technically challenging technique, not only for visualizing the vasculature, but also for performing quantitative diameter and flow measurements. Therefore, MRA protocols need to be adapted for neonates, by shortening scan times to prevent motion artefact, use of low flip angles and out-of-phase imaging in order to better saturate the subcutaneous fat and implementation of ramped radio frequency pulses and multiple thin volume strategies to maintain intravascular signal at the distal cortical branches. Time-of-flight and phase-contrast angiography are the two MRA imaging techniques regularly used to visualize neonatal brain vessels (237, 238).

Electroencephalography (EEG)

The close correlation between cerebral electrical activity and the level of CBF required to maintain neuronal metabolic function, makes monitoring of EEG activity during periods of potentially compromised perfusion to the brain an appealing modality. Analog EEG classically becomes abnormal (suppressed EEG) when CBF falls below 20-25ml/100g/min (239), these EEG abnormalities include: *1) loss of fast beta frequencies (12-30 Hz), 2) slowing of background into 5-7 hertz theta frequencies, 3) slowing into delta range (1-4-Hz), and 4) flattening of the EEG with burst-suppression*. One study showed improvement in the EEG as patients were given hypervolemic therapy, and ischemic conditions improved (240). Although these EEG abnormalities may be present during cerebral ischemia, they are not very specific to cerebral ischemia.

The mean dominant EEG frequency of 6.5Hz was found to correlate with CBF levels of 33-39 ml/100g/min, and when the mean dominant EEG frequency increased to 7.8Hz, CBF improved to 47 ml/100g/min. These results suggest that EEG may serve as a continuous qualitative measure of CBF, assuming that EEG activity is coupled with CBF (241).

Quantitative EEG (QEEG) measures such as compressed spectral array (CSA) and frequency analysis trending have proven more useful in acute ischemic disease, and in particular for critical care physicians not accustomed to interpreting EEGs. Changes in EEG can be quickly identified by changes seen in the QEEG, which allows one to view a smaller portion of EEG for clinical correlation (242). The acute EEG and QEEG, therefore, may provide useful information that can be integrated with other parameters to ascertain changes in CBF in the acutely ill patient.

Somatosensory evoked potentials (SSEP)

The detection of brain ischemia by monitoring SSEPs is an appealing technique, as the somatosensory cortical projections are situated on the hemispheric convexity and are, therefore readily accessible to scalp electrodes. The choice of lower limb (posterior tibial nerve) or upper limb (median nerve) SSEP monitoring may to some extent be guided by the tissue most at risk. At the functional CBF threshold, a further decrease in CBF leads to desynchronisation of cortical neurons, which leads to a decrease in the amplitude, or even disappearance of some peaks on the monitor (243). It should also be noted that SSEP monitoring has a low specificity for cerebral ischemia. SSEP latencies are also less sensitive than amplitudes to a decrease in CBF, because the metabolic needs of axons located in white matter are lower than the neuronal bodies found in grey matter. Hence subcortical structures are more resistant to brain ischemia, owing to lower metabolic needs (244, 245). Quantitative criteria for decreased CBF include: *1) more than 50% decrease in N20 amplitude and 2) an increase in central conduction time (CCT) of more than 1ms or more than 20 from baseline* (246, 247, 248). Qualitative criteria for SSEP alterations have been classified as mild, moderate and severe (249).

Near infra-red Spectroscopy (NIRS)

The use of NIRS for the detection of decreases in oxygenated Hb, and subsequently as a measure of cerebral oxygenation was first reported by Jobsis (93). This technology has shown its usefulness in a variety of clinical applications, including the detection of cerebral ischemia during carotid endarterectomy (96, 97), regional perfusion abnormalities in neonatal cardiopulmonary bypass (98), endoscopic thoracic sympathectomy (99) and cardiopulmonary bypass (100, 101). With regard to its application to cerebral ischemia detection in TBI, it is an appealing method for bedside monitoring of cerebral oxygenation that is both non-invasive and continuous. The infrared beam is generated from a light source and passes through the tissues and is detected by one or more optodes placed a short distance away from the source. NIRS monitoring is based on the fundamental principle that light in the near infrared spectrum (700-1000 nm) will penetrate tissue and that the attenuation of this light is determined by various factors, including the oxidation status of hemoglobin and enzymes in the mitochondrial respiration chain. These characteristics facilitate the ability to measure the concentration of substances within the brain due to the difference in oxygen dependent absorption of near-infrared light passing through (102). The calculation of brain oxygen saturation is determined by comparing the relative concentrations of both types of hemoglobin viz. oxyhemoglobin and deoxyhemoglobin, as derived by their differing infrared absorption capacities.

NIRS is a particularly suitable application for neonates and young children, as their skulls and soft tissue are thinner, compared to adults. NIRS monitoring has progressed quite significantly since earlier days when only simple wave analysis was available. Modern machines are able to provide more data relating to 'spatially resolved' spectroscopy as an absolute measure of cerebral tissue oxygen saturation. However, interpretation of NIRS is subject to much baseline variation, due mostly to individual as well as disease related thresholds. Normal values however, are thought to lie between 60% and 75% (103), but much debate still persists regarding the level and length of time beyond which the damage incurred is irreversible. Therefore NIRS is more helpful when readings are compared to a stable baseline, for

example in cardiac anesthesia and surgery, than in the neurocritical care, where a normal patient baseline may difficult to obtain (250). In TBI, NIRS recording may be adversely affected by subgaleal hematomas, subarachnoid and subdural collections and cerebral oedema (104-106). There are also concerns that NIRS may not be able to detect areas of ischemia (107) and that normal readings have been registered in areas where SPECT scans have demonstrated no CBF and also in dead subjects (106, 108).

Transcranial Doppler sonography (TCD)

The use of TCD in neurosurgery was introduced by Aaslid (161). This device enables non-invasive transcranial measurement of the blood flow velocity in large basal intracranial arteries. Measurements of middle cerebral artery blood flow velocity often are used in the care of TBI patients, and are particularly accurate in the detection of episodes of hypoperfusion induced by low CPP (256). However, it is important to note that TCD provides a measure of CBF velocity and not CBF directly.

TCD is a portable technique that uses a low frequency (2-Mhz), pulsed Doppler transducer to measure the velocity and pulsatility of blood flow within the circle of Willis and vertebrobasilar system (175). Doppler measurement of intracranial blood flow velocity is based on the detection of frequency shifts from insonated red blood cells (RBC) moving through a small, preselected arterial spatial region, 'the sample volume'. This sample volume is determined by the lateral focusing of the transducer and the duration of the transmitted sound burst at a specific pulse repetition rate. The diagnostic accuracy, however, is subject to the knowledge, skill and experience of the user. TCD can be performed on any patient, ambulatory or comatose, so long as they are able to remain stationary in the supine position. The examinations can be performed through four naturally occurring windows i.e transtemporal, transorbital, transforaminal (foramen magnum) and submandibular. Depending on the clinical situation, a complete examination through all available windows may be used, but this is rarely necessary in the context of TBI. The spectrum of intracranial vascular abnormalities in which TCD is useful, includes SAH, vascular malformations, TBI,

brain death confirmation and arterial stenosis. In TBI, vasospasm may occur with traumatic perivascular hemorrhage and may lead to focal or generalized increases in flow velocity, which are detectable with TCD. In absence of vasospasm, high flow velocities may imply hyperemia. Also, disturbances of autoregulation can be examined with TCD by tracking the flow velocity response to changes in blood pressure, as can be the response to CO_2 changes (85, 141).

Insonation of the MCA is usually performed through the temporal window. The depth of insonation giving the highest mean velocity (V_m) is usually chosen. Indices which can be measured are, peak systolic velocity (V_s), end-diastolic velocity (V_d) and time-averaged mean velocity (V_m). These can be used to calculate the pulsatility index (PI), as follows: $\mathbf{PI = (V_s - V_d) / V_m}$ (255). The PI is considered normal if it is between 0.8 and 1.2 (258). Increased PI [>1.2] usually occurs because of increased cerebral peripheral resistance eg. raised ICP or hypocapnia (258, 259). The absolute value of the PI, however, was found to be a poor indicator of raised ICP in children with severe TBI, a high PI in this study seemed to have a stronger association with low CPP (283). A decreased PI [<0.8], may be caused by decreased peripheral resistance or downstream to high grade stenoses eg. arteriovenous malformations (258, 259). The Lindegaard ratio is used to distinguish vasospam from normal blood flow. It relates the MCA blood flow velocity (V_{MCA}) to the blood flow velocity in the ipsilateral extracranial internal carotid artery (V_{ICA}), using the formula : V_{MCA}/V_{ICA}. A threshold value of 3.0 for the V_{MCA} / V_{ICA} index was proposed to differentiate vasospasm from hyperemia (260). A minimal yet significant increase in this ratio, with age, was noted by Krejza et al (261). Using transcranial colour Doppler sonography, they also noticed substantial fluctuations of the V_{MCA} / V_{ICA} index in age-matched male and female groups, suggesting gender related variability in cerebral blood flow velocities. In pediatric patients, poor cerebral hemodynamic status, as evaluated using TCD on admission to the emergency room, correlated with poor prognosis (257).

Table 2. Non-invasive monitoring techniques.

MONITORING TECHNIQUE	ADVANTAGES	DISADVANTAGES	QUANTITATIVE	QUALITATIVE	REFERENCES
PET Scan	1. Provides quantifiable information on CBF, $CMRO_2$ and OEF. 2. Currently considered the 'gold standard' monitoring technique for measuring regional CBF in TBI. 3. Used in conjunction with other focal monitors eg. MD, to provide more detailed information.	1. Need to administer relatively high doses of ionising radiation. 2. The need to transfer sick patients out of a critical care environment. 3. Relatively poor temporal resolution. 4. The need to draw a substantial volume of blood to quantify CBF results.	*		Coles et al-11, Menon et al-12, 111, Bergsneider et al-109, Diringer et al-110, Vespa et al-142, Volpe et al-282,
Xenon-CT (Xe-CT)	1. Provides multislice CBF images. 2. Provides quantitative values of CBF and CVR (when combined with acetazolamide). 3. The technique is based on CT, which is a ubiquitous technology. 4. The hardware and software are relatively inexpensive. Challenge tests can be performed to study	1. High dose of radiation due to repeated CT scans. 2. Xenon is thought to cause raised ICP, EEG changes and a decrease in CBF. 3. Has limited temporal resolution. 4. Patient motion can produce artifacts, making interpretation difficult.	*		Mallett et al-115, Heinz et al-116, Norman et al-117, Obrist et al-119

	cerebrovascular physiology				
SPECT	1. SPECT imaging is relatively easy to perform. 2. Semi-quantitative measurements can be obtained rapidly. 3. Most large radiology department have adequate hardware and software. 4. The software provides three orthogonal views of CBF in colour.	1. The technique has poor spatial resolution, compared to CT and MRI scans. 2. The data are non-anatomic, requiring correlation with either CT or MRI scans. 3. There is no standard with which to compare the counts in a given ROI. 4. Poor specificity, as the same SPECT pattern may encountered in different pathologies.		*	Catafau-183, Catafau et al-185,186, Sugawara et al-184, Lassen et al-187, Ichise et al-188
PERFUSION CT	1. The technique is based on the use of helical and spiral CT scanners, which are relatively accessible. 2. Ability to qualitatively measure CBV and MTT and quantitatively assess various degrees of ischemia. 3. Ability to evaluate the efficacy of revascularisation procedures. 4. Perfusion CT	1. Accuracy of flow values are not yet fully validated. 2. Requires intravenous access and administration of iodinated contrast agent. 3. Limited spatial coverage. 4. The radiation dose to the volume of tissue studied is relatively high, compared to	*	*	Hoeffner et al-193, Nabavi et al-191 Koenig et al-189, Wintermark et al-190, 192, 196

	studies do not require any special equipment.	other perfusion techniques.			
MRI SEQUENCES	1. The ability to image not only cerebral perfusion, but also the status of the tissue (diffusion), the patency of the vasculature(MRA), and the anatomical substrate during the same imaging session. 2. The ability to differentiate reversible and irreversible ischemic tissue by defining the status of the tissue via DWI, relative to its perfusion. 3. The acquisition of many data points per voxel, which increases the quality of the time-dependent calculations. 4. No radiation dose required.	1. The equipment is expensive. 2. The lengthy duration of the examination.	*	*	Rutherford et al-230,233, 237, Bykowski et al-232, De Vries et al-234, Harris et al-235, Green et al-236, Tanner et al-238
NIRS	1. Portability allows bedside monitoring in the ICU. 2. Real-time recordings. 3. Useful in a number of clinical applications eg. TBI, SAH, carotid	1.Controversy remains over which tissue(scalp or brain) is responsible for light attenuation in NIRS. 2. Limited spatial resolution.	*	*	Kirkpatrick et al-250, Roberts et al-97, Daubeny et al-100, Smith et al-103, Al-Rawi et al-104, Buchner et al-105, Schwarz et al-

	endarterectomy. 4. Can be used as part of multi-modality monitoring in TBI.	3. Difficulty with quantification algorithms.			106
TCD	1. Relatively easy to use. 2. Most units are quite compact, making portability and bedside testing easy. 3. Can provide measurements of both anterior and posterior circulation. 4. Used in multi-modality monitoring to help interpret perturbations in other parameters.	1. Accurate interpretation of readings, requirescorrelation with other monitoring techniques. 2. Readings are user dependent.		*	Aaslid et al-161, Harders et al-175, Trabold et al-257, Ract et al-255, Hassler et al-258, Lindegaard et al-260, Krejza et al-261, Figaji et al-283
EEG	1. Provides information on the function of brain tissue which depends on both CBF and metabolism. 2. Easy to implement in ICU/theatre 3. Relatively inexpensive. 4. Quantitative EEG provides information about ischemic injury.	1. Lack of etiological specificity. 2. Influenced by anesthesia and hypothermia. 3.Interpretation is quite subjective and user dependent.	*	*	Florence et al-243, Prior et al-244, Lam et al-247, Thiel et al-248
SSEP	1. Provides information on the function of brain tissue which depends on both CBF	1. Lack etiological specificity. 2. Influenced by anesthesia and	*	*	Kearse et al-251, Lam et al-247, Thiel et al-248, Guerit et al-249

	and metabolism. 2. Easy to implement in ICU/theatre 3. Relatively inexpensive. 4. Requires less electrodes than EEG.	hypothermia. 3. Interpretation is quite subjective. 4. Provides less data than EEG.			

Discussion

It is clear that there are many ways to diagnose and monitor aspects of CBF patterns and oxygenation in the injured brain. The various modalities discussed above, each have distinct advantages, which encourage their continued use in the setting of TBI, however each of these have significant limitations, so there is no ideal monitor for brain perfusion and oxygenation in TBI.

Recent literature still favours the use of PET scanning as a comparative standard. In some centres this is combined with MD recordings, as the current 'gold standard' for measuring CBF and detecting global cerebral ischemia (11, 109, 110, 111). There is however a growing body of evidence in favour of $PbtO_2$ monitoring (71, 73, 74, 75, 76, 77, 176, 178, 179) as a useful tool, particularly when used in conjunction with ICP monitoring, for continuously assessing the adequacy of brain tissue oxygenation. Although it is not an ischemia monitor, it may play a useful role in the detection of ischemia because ischemia is an important cause for low $PbtO_2$. The specific diagnosis of ischemia, however, will depend on the use of ancillary investigations.

The context of monitors such as $PbtO_2$ is fundamentally different to that of the various imaging modalities. $PbtO_2$ is used as a monitor in the neurocritical care unit, while PET and other imaging modalities are used primarily as a research tools or for more information at a single point in time. The bedside continuous monitors may be limited in the information they can provide and their spatial resolution is poor. On the other hand, imaging modalities have better spatial resolution, and may provide very detailed information, but have little temporal resolution in a condition that is highly dynamic. Arguably, a better understanding of the pathophysiological

changes in TBI, for example brain ischemia, may be achieved by combining the information that one gets from these different modalities, rather than relying on a single modality, or group of modalities, for precise answers.

The ideal monitoring modality would be non-invasive, provides continuous real-time recordings, good temporal and spatial resolution, is inexpensive, easy to use and interpret and does not require transfer of the critically ill patient out of the ICU. While such a monitoring modality remains elusive and probably unlikely, in reality, the best way to monitor the management of TBI patients probably lies in employing a multimodality approach, aiming to combine information regarding regional and global CBF patterns, ICP and oxygenation. While the combination of these various modalities continue to provide information about the state of CBF, the parameters they measure differ, and the values suggested by some of the more important studies on the subject differ as well. The relevant studies examining the occurrence of PTCI will be discussed in the next chapter.

CHAPTER 5: Literature review of clinical studies assessing cerebral ischemia in traumatic brain injury.

Early reports describing ischemia as an important secondary insult in severe TBI were based on the histopathological findings in postmortem studies of TBI. The antemortem diagnosis of secondary ischemia however, has proved more elusive and controversial. Recent studies addressing the issue have variably used PET scanning or Xe-enhanced scanning techniques, microdialysis and $PbtO_2$, but there are substantial differences between imaging and ICU monitoring techniques, as discussed previously.

There is variability in the risk of ischemia reported in these studies in part due to differences in the methodologies used, timepoints evaluated, and definitions of ischemia. This section reviews some of the important studies on secondary injury, including ischemia, in adult and pediatric TBI to highlight the major issues. It is divided into five parts, viz. studies based on histopathological findings, studies based on PET and MD findings, studies based on Xe-CT findings, studies assessing both $SjvO_2$ and $PbtO_2$ in TBI, and finally studies that were specifically pediatric in nature. The key findings of these studies provided in Table 3.

i) Studies based on histopathological findings

Early reports on the post-mortem appearances of ischemia in fatal head injuries emanated from the seminal work done by Graham and Adams (13). In this study, published in 1978, the authors set out to determine the incidence and distribution of ischemia related brain damage in patients who died as a result of non-missile head injury. They performed both neuropathological and neurohistological examinations on 151 consecutive post-mortem specimens from patients who died due to severe head injury. The authors documented ischemic damage in 91% of cases, after excluding cases where necrosis and infarction were related to contusions or fat embolism and cases where infarction of the brainstem was thought to be typically

due to raised intracranial pressure. In 27% of these cases, the ischemic damage was found to be severe, in 43% it was found to be moderately severe and in 30% was found to be mild. The anatomical regions in which these areas of infarction were concentrated were, the hippocampus, basal ganglia and cerebellum. The authors also demonstrated a statistically significant correlation between demonstrated ischemic brain damage and, either an episode of hypoxia or raised ICP. The findings in this seminal paper demonstrated that ischemic brain damage is common after head injury, and is at least in part, potentially avoidable. It was also one of the earliest studies to highlight ischemic brain injury as an important cause of morbidity and mortality after head injury, as well as to attempt to demonstrate the frequency of ischemia in head injury (22). However, because these were postmortem data, the results of the study did not provide an understanding of the incidence of secondary ischemia in survivors of TBI or quantify the risk in patients being actively managed in the neurocritical care unit. So the question remained: was secondary ischemia a major finding only in patients who died because of severe TBI, or was it a common and potentially preventable secondary injury in all patients with severe TBI?

ii) Studies using Xe-CT scans

A study by Bouma et al (15), suggested that while the role of ischemia in TBI was important in fatal head injury (13,14), CBF studies done subsequently, had failed to demonstrate this as a common occurrence. Therefore they postulated that the measurement of CBF in these studies had not been performed early enough to detect cerebral ischemia, i.e. during the period of highest risk for posttraumatic ischemia. In their study, they used Xe-CT scans and $AVDO_2$ measurements, aiming to evaluate the occurrence of ischemia early in head injury by performing the initial measurements within the first 6 hours post injury. Their results suggested global ischemia (CBF<18ml/100g/min) in 12.9% of patients, at some point after injury. They also demonstrated, however, that in the first 4-6 hours post injury, the mean CBF was lower than at any point thereafter and that critically low CBF (<18ml/100g/min) was found in 33% of these cases. They also found that early

cerebral circulation and metabolism disturbances i.e. within the first few hours post injury, were the most important factors correlating with both clinical status (motor score in the GCS) and outcome. The limitations to this study were that the decrease in CBF demonstrated, may not actually reflect an inability to meet the metabolic demands of the tissue, but may reflect decreased $CMRO_2$ coupled with CBF found after head injury. The fact that all patients who had intracranial mass lesions were not evaluated, due to the obvious need for urgent surgical evacuation also excluded a significant segment of patients. The Xe methodology used in this study also has a relatively poor spatial resolution and may therefore miss significant areas of regional or focal ischemia. These shortcomings need to be borne in mind when interpreting these results.

Another important study by the same group in 1992 (159), aimed to perform 'ultra early' CBF measurements. The method of measuring CBF in this study, differed from that of the previous study, in that the stable Xe-CT method used in their later study is considered to have a higher spatial resolution and therefore allows for a more precise correlation between flow and anatomy. The time after injury at which the studies were performed, ranged from 50 minutes to 8.5 hours (mean of 3.1 hours). The overall incidence of cerebral ischemia, both regional and global, in this series was 31.4%. This figure is slightly lower than the 33% shown in the previous study and contradicts the speculation made in that study, that "with earlier measurements (<4 hours post injury) an even higher incidence of ischemia would be found". The possible reasons suggested by the authors for this discordance was that a relatively large number of patients with normal CT scans, who followed commands within 48 hours, in this group, would probably have been excluded from the previous group and that this group did not include some of the most seriously injured patients with mass lesions, as they were taken to theatre immediately after the initial CT scan.

iii) Studies done using PET scans and MD.

A study by Vespa et al in 2005 (142) examined the subject of metabolic dysfunction in relation to ischemia in 19 adult TBI patients using PET and microdialysis (MD) at a mean time of 36 hours post injury. The latency from injury to PET was 60 ± 30 hours after injury. Using PET, they were able to examine regional CBF, OEF, $CMRO_2$ and cerebral metabolic rate of glucose (CMR_{glu}). The parameters used to define cerebral ischemia in this study, were an OEF > 0.75, coupled with a cerebral venous oxygen content (CvO_2) <3.5ml/100ml. Microdialysis parameters included the lactate/pyruvate ratio (LPR) and cerebral glucose levels. These were also used in the definition of ischemia or mitochondrial dysfunction viz. glucose < 2mmol/L and LPR > 40, as initially proposed by Landolt in 1994 (90). The results of this study suggested a prevalence of post-traumatic ischemia of 1% of total brain volume (TBV). However, the frequency of metabolic dysfunction was higher, which the authors termed 'metabolic crisis without ischemia', implying mitochondrial dysfunction without necessarily a substrate delivery problem. These findings were similar to those from a study by Diringer et al (141), which examined the regional cerebrovascular and metabolic effects of hyperventilation after TBI. The OEF, CBF and $CMRO_2$ values at a baseline arterial carbon dioxide ($PaCO_2$) concentration of 40mmHg were similar in both studies. The findings of the Vespa et al (142) study showed a lower mean ischemic brain volume (IBV) of 1.5cm^3, which translates into 1.5% of total brain volume. Limitations of this study, however, include the following: the PET scans were performed at later time points after injury when compared to other studies, with imaging performed at a mean time after injury of 36 hours. This limitation means that earlier episodes of ischemia during a higher risk period may have been missed. Importantly, these results also reflect a single point in time, whereas acute TBI is a dynamic condition. Finally, PET scans require patients to be stable before transport to the imaging facility, which may select patients at times that are relatively lower risk for ischemia.

Another important PET study was reported by the Cambridge group (11) in 2004. The results from this study were based on PET imaging data used in combination

with arterial tracer activity measurements and jugular bulb specimens. These findings were used to assess CBF, CBV, $CMRO_2$ and OEF. PET studies were undertaken in both normal volunteers and head injury patients, within 24 hours of injury. The burden of ischemia was ultimately assessed using the OEF. The benefit of using OEF is that the confounding effects of drug and injury induced metabolic suppression on CBF and $CMRO_2$ are avoided. The OEF values used to define critical ischemia in this study, were based on a formula using CaO_2 values from arterial samples, then subtracting CvO_2 from these values. CvO_2 was identified as a critical predictor of infarction in experimental ischemia values below 2.9ml/100ml (143). These OEF thresholds were then used in applications to facilitate the calculation of the volume of voxels with a CvO_2 value below this threshold and hence allowed estimation of the ischemic brain volume (IBV). The IBV data was then compared to data derived from $SjVO_2$ samples using traditional threshold values for $SjvO_2$ and $AVDO_2$ (50% and 9ml/100ml, respectively) (144-148). The results showed a significantly lower CBF and $CMRO_2$ and a higher CBV and OEF value in the head injury patients, when compared with the control group. The estimated IBV was also higher in the head injury group, with ischemic values of between 1 – 16% of total brain volume (TBV). These 'ischemic voxels' seen on the PET images, were found mostly adjacent to contusions or intracranial hematomas (ICH) in the frontal, temporal and parietal regions. Of note the $SjvO_2$ threshold in the presence of ischemia was higher than that described in previous studies (144, 147). $SjvO_2$ values of 50 % were only found when a substantial proportion of the brain was potentially ischemic, approximately 170 ml, which equates to about 13% of the TBV. The investigators also emphasized the fact that PET imaging represented a snapshot of the brain metabolic state and while it does provide an indication of the burden of ischemia at the time of imaging, it does not take into account of the duration of such ischemia. This means that transient ischemic events eg. focal seizures, may temporarily increase oxygen demand during the scan and subsequently cause an increase in OEF resulting in the IBV overestimating the burden of ischemia. Conversely, ischemia may develop at other times during the patient's illness and adversely affect outcome, but would remain undetected during a single scan. The

'snapshot' IBV figure would therefore underestimate the overall burden of ischemia over the course of the patient's illness. The data in this study does suggest that while high OEF values may represent ischemia, the pathophysiology may be more involved than that seen in ischemic stroke. The coexistence of relative ischemia and hyperemia in some patients may represent a more fundamental problem with matching of perfusion to oxygen use after head injury. A recommendation made by these authors is that other imaging modalities such as proton magnetic resonance spectroscopy (^{1}H MRS) be used at follow up to validate the thresholds used to define critical ischemia. The authors suggested that OEF provides the only valid indicator of the adequacy of CBF and oxygen delivery and is independent of $CMRO_2$. A high OEF was found to denote an imbalance of flow–metabolism coupling, which is characteristic of tissue at high risk of ischemic injury.

A later PET study by the same group, also in 2004 (111), demonstrated that hypoxic regions in the injured brain may be less able to increase OEF than previously assumed, due to 'diffusion barriers' which limit oxygen diffusion in the injured brain. They used $PbtO_2$ values of less than 10 mmHg to define the ischemic threshold for tissue. $SjvO_2$ values were used to calculate the $AVDO_2$. Controlled hyperventilation was used to decrease the CBF, and the $PbtO_2$, $AVDO_2$ and OEF calculated for the hypoxic regions of the brain, demonstrated an attenuated ability to increase OEF. They concluded that global or regional OEF, as a marker of hypoperfusion, underestimates the burden of ischemia in TBI.

iv) $PbtO_2$ and $SjvO_2$ studies

$PbtO_2$ and $SjvO_2$ studies are worthwhile examining, because even though they are not necessarily ischemia monitors, they are both continuous monitors that may detect ischemia in the ICU. A study by Rosenthal et al (158), using $PbtO_2$ and CBF monitoring modalities, evaluated whether $PbtO_2$ more closely reflected cerebral oxygen diffusion or cerebral oxygen delivery and consumption. They investigated 14 TBI patients, using a combination of an oxygen challenge, MAP challenge and hyperventilation challenge, to assess tissue oxygen reactivity, autoregulation and

cerebral vasoreactivity, respectively. The findings from this study suggest that $PbtO_2$ is most closely related to CBF and $AVDO_2$, and this implies a relationship between the amount of dissolved plasma oxygen and the oxygen concentration in brain tissue. The authors found this to be consistent with their hypothesis that it is the diffusion of dissolved plasma oxygen, rather than total oxygen delivery, that is related to $PbtO_2$. This suggests that $PbtO_2$ is not an ischemia monitor per se, but rather that low $PbtO_2$ values are more complex, and in particular may be affected by low CBF, low PaO_2, and oxygen diffusion through the tissue.

Hlatky and colleagues (149) evaluated the monitoring and treatment of intracranial hypertension and cerebral ischemia as secondary injury processes in the injured brain. Several factors were highlighted as contributing to PTCI. These included systemic arterial hypotension, increased ICP, cerebral oedema, focal tissue compression from hematomas and microvascular diseases. The authors therefore suggest that the ideal monitoring technique for cerebral ischemia would give regional information about CBF as well as providing continuous information about the evolution of CBF over time after injury. They divide the available techniques into two categories, viz. techniques based on perfusion and techniques based on adequacy of flow. The most widely used of the latter group are the $SjvO_2$ and $PbtO_2$. Both of these techniques are indicative of the adequacy of flow relative to the cerebral metabolic requirements in the involved region of the brain. While raised ICP is quoted as the most common cause of $SjvO_2$ desaturation in this study, a major limitation of $SjvO_2$ monitoring is its limited ability to identify regional ischemia. In conditions like TBI where there is considerable regional heterogeneity of CBF pattern, monitoring of $PbtO_2$ is suggested as more advantageous, in this study. The normal values for $PbtO_2$ listed in this study are approximately 20 to 40 mmHg, with a critical threshold of 8 to 10 mmHg.

A study by Kiening et al (67), correlated an $SjvO_2$ of 50% with a $PbtO_2$ of 8.5 mmHg. The authors suggested this value as a critical threshold. They conclude by suggesting that stable Xe-CT be used to obtain intermittent measurements of regional CBF, if no hypoperfused regions are detected via this modality, then a global monitor such as

$SjvO_2$ was suggested. If significant heterogeneity of flow was demonstrated, however, $PbtO_2$ monitoring was recommended as the preferred monitoring modality. Whichever of these modalities were ultimately chosen, using the abovementioned recommendations, would then to be used in conjunction with ICP monitoring.

v) Pediatric specific studies

Clinical studies aimed at demonstrating the pathophysiological changes occurring after severe TBI, have involved mainly adults, with pediatric TBI representing only a small proportion of the population. An understanding of the dynamic nature of the pathophysiology of TBI (both in children and in adults) is fundamental to a rational management protocol, particularly aimed at the prevention or amelioration of secondary injury.

Early studies suggested that increased CBF (cerebral hyperemia) was a common occurrence in pediatric TBI (284, 290, 291). In a study investigating the relationship between CBF, $AVDO_2$ and $CMRO_2$ in pediatric TBI, Sharples et al (285) found increased CBF after severe TBI in children to be an uncommon finding. They also demonstrated an inverse relationship between raised ICP and CBF, as well as a fall in $CMRO_2$ with time, suggesting that $CMRO_2$ may be at its highest early after TBI. These findings, taken in context of the study by Bouma et al (15), as discussed earlier, suggest that the risk of ischemic brain injury may be highest in the first few hours after TBI.

In another paper by the same group (286), the role of cerebrovascular resistance (CVR) in pediatric severe TBI was explored. They found a significant correlation between cerebrovascular resistance and CPP, concluding that pressure autoregulation in this group of patients was often intact. They also found $CMRO_2$ to be a strong determinant of CVR, which was interpreted as reflecting appropriate metabolic coupling in this group of patients. This finding was in contrast to data published by Muizelaar et al (287), who suggested that metabolic uncoupling after

TBI was a significant occurrence. The main reason postulated by the authors (286) for this disparity, was that Muizelaar et al had compared their $AVDO_2$ results with normal values in adults, as opposed to normal $AVDO_2$ values in children. In both the studies published by Sharples et al (285, 286), they suggest that "the pathophysiology of TBI in children is essentially not different from that in adults".

The results of the study by Muizelaar et al (287) demonstrated hyperemia in a significant number of the CBF measurements they conducted (88%). CBF and metabolism were found to be completely uncoupled 24 hours post-TBI, as demonstrated by a high CBF and low $AVDO_2$. The lack of a clear relationship between CBF and CBV, led to the conclusion that increased CBV may play an important role in pediatric TBI, even though it may not always be accompanied by a high CBF. The authors also did not support the contention that vascular factors play a stronger role than CSF factors in determining ICP after TBI, as suggested in an earlier study (291).

A recent study (76) using $PbtO_2$ monitoring in children with severe TBI (GCS ≤8) examined the association between various patient factors, including $PbtO_2$, with outcome. The main findings of this study were that episodes of low $PbtO_2$ (in particular, $PbtO_2$<10 mmHg) were found to have an independent association with mortality and poor outcome (measured by the Glasgow Outcome Score and the Pediatric Cerebral Performance Category Scale), $PbtO_2$ was reduced to lower values and for longer periods of time in patients who had a poor outcome. $PbtO_2$ also appeared to have a stronger association with outcome than ICP and CPP in multivariate analysis. Thus $PbtO_2$ tends to have a similar association with outcome in children as in adults. The above study was not able to determine a difference in $PbtO_2$ thresholds across age ranges, however, it is possible that the sample size was too small and that larger numbers are required in each age group to detect meaningful differences.

Table 3. Summary of literature review.

Author	***Date of publication***	***Modality used***	***Sample size***	***Adult or pediatric***	***Time of assessment***	***Main findings***	***Limitations of study***
Graham and Adams-13	1978	Post-mortem histology	151	Adult	Post-mortem	Ischemia was a common finding (91%) in fatal traumatic brain injury	Studies performed on post-mortem specimens, therefore the application of these findings to antemortem or non-fatal TBI cases has been a subject of much contention.
Bouma et al-15	1991	Xe-CT	186	Adult	Within 12 hours of injury (earliest was within 4 hours)	Low CBF (<18ml/100g/min) was most frequent in the 1st 6 hours post injury, and critically low CBF was found in 33% of patients.	Intermittent measurements may miss short-lived episodes of ischemia. The effect of acute intracranial hematomas, as these patients underwent craniotomy prior to their first CBF study, was not accounted for. Xe-methodology has poor spatial resolution. Xe-CT cannot adequately assess CBF in deeper areas of the brain.
Coles et al-11	2004	PET scan	25 (10 healthy subjects and 15 TBI patients)	Adult	Within 24hours of injury	Regional ischemia (6% of TBV) is present in early head injury, even where suggested targets of ICP and CPP are achieved. Bedside monitoring techniques, like jugular bulb oximetry may miss clinically important regional ischemia, which is potentially related to outcome.	PET imaging provides a snapshot of the brain's metabolic state and therefore has poor temporal resolution. The statistics in such voxel-based measurements are less robust than those from larger regions of interest and may also be more susceptible to reductions in signal-to-noise

							ratios. Regional / focal ischemia may still be missed by a global monitor.
Kienin g et al-67	1996	SjvO2 and PtiO2	15	Adult	SjvO2-within 6-24hours post-injury PtiO2 - within 12 hours post-injury	For SjvO2-a hypoxic threshold of 50% was found to correlate with a PtiO2 of 8.5mmHg (3-12mmHg). Brain PtiO2 monitoring was found to be a useful addition to existing neuro-monitoring methods.	Small number of patients may limit interpretation of results. True tests for pressure autoregulation were not performed.
Menon et al-111	2004	PET, Cerebral tissue PO_2 (PtO_2) and Electron microscopy – to examine pericontusional tissue.	13	Adult	PET studies - within 2-7 days of head injury.	In TBI, hypoxic regions may be less able to increase OEF, due to an increased gradient for oxygen diffusion (due microvascular collapse/endothelial swelling/perivascular oedema). Hypoxic cell death may therefore not be solely due to simple hypoperfusion, and the burden of ischemia in the injured brain may be underestimated, when using techniques reliant on cerebrovascular adequacy, such as OEF and SjvO2.	The ischemic threshold chosen, of 10 torr (1.35kPa), is not universally accepted. The results may therefore have been attributable to the selected threshold. The nature and volume of tissue sampled by the oxygen sensor, may also influence results.
Vespa et al-142	2005	PET and MD	19	Adult	Within 12-115 hours (mean 36hours)	This study demonstrated that the incidence of ischemia, as measured by conventional PET scan (also as defined by other clinical monitors, ie, PbtO2 and SjvO2) is low, viz. 1.5% of TBV. The metabolic abnormalities demonstrated by the various MD analyses,	PET studies were performed at later timepoints post injury, when compared to similar studies. Within subject baseline and hyperventilation studies were not performed. PET is a 'point in time' modality, hence it provides a snapshot

						however, show that a metabolic crisis is common after TBI, despite the low incidence of ischemia.	representation of a dynamic injury process.
Bouma et al-159	1992	Xenon CT	35	Adult	Within 50 minutes -8.5 hours post injury.	The overall incidence of ischemia (both global and regional) in this series, was 31.4%. This finding confounds the speculation by the authors in their previous study (15), that 'with earlier measurements i.e. within 4 hours, even higher incidence of ischemia would be found. They also found no association between the occurrence of ischemia and the presence of hypoxia or hypertension on admission.	Even though the authors concluded that the inhalation of 32% stable xenon over 4.5 minutes had no adverse effects on CBF and ICP, there are still serious concerns regarding the use of xenon. This series contained a relatively large number of patients with normal CT scans, which makes comparison with the previous study difficult.
Sharples et al-285	1995	Modified Kety and Schmidt technique (using 10% NO) Arterial blood gas(ABG) $SjvO_2$	21	Pediatric	Range: 5.75-50 hours post injury	Absolute cerebral hyperemia is an uncommon finding in pediatric severe TBI. Raised ICP was associated with low CBF. Children with severe TBI may be most at risk of sustaining ischemic brain damage in the first few hours, as low CBF appeared to be accompanied by a higher $CMRO_2$.	Relatively small number of patients in the study. Patient ages range from 2-16 years old, likely developmental changes in CBF and $CMRO_2$ were not accounted for. CBF and $AVDO_2$ values were not corrected pCO_2, making comparison with similar studies more difficult.
Sharples et al-286	1995	Modified Kety and Schmidt technique (using 10% NO)	21 (17 patients who had CBF, CMR	Pediatric	Range: 5.75-50 hours post injury	Normal autoregulatory mechanisms, particularly metabolic autoregulation, are preserved in most children with severe	Relatively small number of patients in the study. Patient ages range from 2-16 years old, likely developmental changes in CBF and

		Arterial blood gas (ABG) $SjvO_2$	O_2 and ICP monitors			TBI. The subpopulation in whom pressure autoregulation appeared to be impaired, may be particularly susceptible to cerebral ischemia. Authors suggest that the pathophysiology of TBI in children is similar to that in adults.	$CMRO_2$ were not accounted for. CBF and $AVDO_2$ values were not corrected pCO_2, making comparison with similar studies more difficult. Findings in a pediatric study may not be true in an adult population.
Muizelaar et al-287	1989	Xe inhalation method ABG $SjvO_2$	32	Pediatric	Mean time: 11±3 hours post-injury.	Hyperemia was demonstrated in 88% of CBF measurements. CBF and metabolism were found to be completely uncoupled 24 hours after injury. Lower CBF values early after TBI seem to be related to poor outcome. No clear relationship between CBF and CBV.	Results represent global blood flow and thus may miss regional ischemia. Normal CBF values in children were not well established, using the Xe inhalation method.
Figaji et al-76	2009	$PbtO_2$ monitoring	52	Pediatric	Mean time: 13±15.4 hours after injury.	Episodes of low $PbtO_2$ showed an independent association with poor outcome and mortality after pediatric severe TBI. $PbtO_2$ appeared to have a stronger association with outcome than ICP and CPP.	Age range of patients (9months to 14 years old) may require examination for age-related differences in threshold tolerance. This was not a purely observational study, as interventions were effected for raised ICP, low CPP and low $PbtO_2$. The effect of interventions for low $PbtO_2$ were not examined.

Discussion

The disparity between the findings in the studies using different methodologies to examine the problem of secondary cerebral ischemia after TBI is quite apparent. The earlier histopathological studies suggest that the occurrence of PTCI is very high, at least in fatal cases, with ischemic damage documented in 91% of cases. Studies using Xe-CT suggest a frequency of between 12.9% and 33%. Data from PET and MD, suggest a much lower frequency of PTCI than others, they however define their results in terms of IBV, with figures of between 1% and 6% of TBV.

The findings in these studies are affected by numerous factors, which revolve mostly around what is being monitored and the temporal and spatial resolution of the monitoring modality. The timing of the investigation is an important feature, as the risk of ischemia seems to be higher in the early post injury phase (15). The heterogeneity of CBF patterns in the post injury phase, increases the difficulty, as global methods may miss regional ischemia and the reliability of focal methods, depend on appropriate selection of the site for monitoring. The paucity of literature specifically relating to pediatric TBI, its pathophysiology and age-related changes, make this area of study particularly challenging.

Despite the limitations of point-in-time imaging modalities, PET scans remain the 'gold standard' modality in the detection of cerebral ischemia, and have provided some of the most reliable data to date. The results yielded by the most recent studies using this modality, have suggested a relatively low prevalence of ischemia, but this may be limited by the aforementioned factors peculiar to PET scanning.

This leads to the central aim of the present work: to examine how single datapoints of $PbtO_2$ measurements (a widely used modality) in patients with TBI, taken at discreet timepoints post-TBI, compare with each other and with the overall frequency of 'adverse' $PbtO_2$ events over the full duration of monitoring. In essence this would use a single technology and compare a snapshot technique with data available from continuous monitoring. The hypothesis of the study is that events that may be detected at a single point in time after TBI depend on the timing of the

study, and may not reflect the overall risks of these events occurring over the full duration of the period at which the patient is at risk.

CHAPTER 6: Study design, research methods, results and discussion

Objective

It is generally believed that cerebral ischemia, or brain hypoxia is an important contributing factor to secondary injury and poor outcome in TBI. Point-in-time imaging techniques may have good spatial resolution and can examine more aspects of brain perfusion and metabolism than continuous monitors but cannot quantify the overall burden of the problem over the full time period during which the brain is vulnerable to these insults because TBI is a highly dynamic condition. Often these studies can only be performed in patients who are stable enough, both for transport and for prolonged imaging, whereas unstable patients, who are more likely to be at risk of adverse secondary events, are usually not imaged. Therefore these investigations may not give the treating physician a sense of how common these potentially injurious events may be. This is important because some studies suggest a relatively low prevalence of ischemia after TBI (11, 15, 142, 159). Other modalities used in the ICU may give less information than imaging techniques and may be more spatially limited, but have the advantage of being able to monitor the patient continuously. These appear to suggest a higher burden of events that may be ischemic in nature in TBI patients (13, 14, 75, 76). The discrepancy may lie not only with the methodology used, but also the fact that one is comparing frequencies reported at a single point in time with frequencies determined from monitoring continuously over the full duration of the acute period after TBI.

The purpose of this study is to examine the relationship between the frequency of adverse events occurring at 2 selected time points post-severe TBI in comparison with the overall frequency of these events occurring over the full duration of monitoring. To do this, a retrospective study was undertaken of a large cohort of children with severe TBI. $PbtO_2$ monitoring was selected as a single monitor to examine these data. Although a $PbtO_2$ monitor is not an ischemia monitor per se, evidence is accumulating that episodes of low $PbtO_2$ are associated with poor

outcome and so it appears to represent a means of detecting adverse secondary events after TBI, of which cerebral ischemia is one. As such it would be useful as a continuous monitor for the assessment of the burden of these events over a prolonged period of monitoring. Although the data cannot be compared directly with the data from imaging studies, one would expect that it should reveal some of the dynamic nature of changes in TBI, the principles of which should apply to data derived from studies performed at a single point in time.

Study design

This study was a retrospective review of prospectively collected data of children with severe TBI who received a $PbtO_2$ monitor. All data were obtained from the neurotrauma database at the Red Cross War Memorial Children's Hospital. Informed consent was taken for monitoring of each patient from the parent or guardian of the child. Approval for the work was obtained from the Human Ethics Board of the University of Cape Town.

Methods and materials

All children who sustained a severe head injury (post resuscitation GCS ≤8), or who deteriorated to this level after admission were admitted to the ICU and considered for invasive monitoring, including a $PbtO_2$ monitor, unless the patient was improving and it was anticipated that early extubation could be achieved. These patients were then managed in the ICU using an institutional protocol aimed at preventing secondary injury, based on the current Guidelines for the Management of Severe TBI in Children and Adolescents (288, 289).

Significant mass lesions were removed surgically as soon as possible. ICP and $PbtO_2$ monitors were inserted in the operating room or by the bedside in the ICU. General therapy was aimed at controlling ICP and optimizing CPP. ICP was measured using a parenchymal monitor [Codman ICP Express (Codman, Raynham, MA, USA) or Camino (Integra Neurosciences, Plainsboro, NJ, USA)]. ICP was treated when it was

increased to > 20mmHg for more than 5 minutes. Treatment was instituted in a stepwise manner, first using basic measures such as sedation +/- paralysis, hyperosmolar therapy (hypertonic saline or mannitol), and ventricular drainage (where possible), and then proceeding to second-tier therapy if the increased ICP was resistant to these measures. These second tier therapies included barbiturate coma and decompressive craniectomy. In general, CPP was maintained greater than 50mmHg in older children, or greater than 45mmHg in children less than 2 years old. The approach to maintenance of CPP was influenced by the status of autoregulation, the $PbtO_2$ recording, and whether there was underlying respiratory injury.

$PbtO_2$ monitoring and treatment: The $PbtO_2$ monitor was usually placed in right frontal white matter that appeared relatively uninjured on the head CT scan, or on the side of greater injury. Occasionally, in patients with focal injury, a $PbtO_2$ monitor was placed in a peri-contusional location, this was the case in a very small number of patients and did not warrant a subgroup analysis. All patients underwent head CT scanning after monitor insertion to confirm location of the probe. The treatment target for $PbtO_2$ was 20mmHg. In general, more aggressive measures to increase $PbtO_2$ were used when $PbtO_2$ decreased to below 10-15mmHg. The approach to treating reduced $PbtO_2$ began with a search for possible causes, including increased ICP or reduced CPP, systemic hypoxia or hypercarbia, anemia, subclinical seizures, or vasospasm. Measures used to increase $PbtO_2$ depended on the patient's condition and were individualized. In general, these included more aggressive treating of ICP, when ICP was borderline, increasing CPP when safe, blood transfusion, increasing $PaCO_2$ when ICP was not significantly increased, and increasing the inspired fraction of oxygen.

All data from the intracranial monitors were monitored continuously and recorded hourly. More recently, data were also recorded continuously at a sampling frequency of 50 Hz using a dedicated data collection system (ICMPlus®, Cambridge

University). Patients were monitored until their ICP and $PbtO_2$ readings remained stable for 24-48 hours and extubation was planned.

Data analysis

$PbtO_2$ data were analysed at two specific time-points after the time of injury, i.e. early and late. The 24 hour time-point after injury (early) was selected to represent a relatively early post-injury time that still took advantage of the fact that monitoring in many patients started after 12 hours post-injury. The 72 hours after injury (late) time-point was selected to represent a time-point midway through the post-injury course. In addition, the first 24 hours of $PbtO_2$ monitoring was examined, as well as a 24-hour period around the 72 hour mark, i.e. from 12 hours before to 12 hours after the 72 hour mark. All data were analysed only after a 2 hour run-in period for the monitor had elapsed, to avoid any artefactual data from a $PbtO_2$ monitor that was still stabilizing. Although our treatment threshold for $PbtO_2$ treatment is 20mmHg, $PbtO_2$ < 10mmHg was selected for analysis as a measure of low $PbtO_2$ because of the stronger association with outcome in adult and pediatric studies, including data from our own institution, and because of laboratory data showing a strong association with CBF decreased below critical thresholds (67, 76, 148, 150,). Additional data recorded included clinical data (neurological examination and systemic injuries), arterial blood gas results, the inspired fraction of oxygen on the ventilator, serum sodium, MAP and ICP.

Patients were excluded from analysis if 1) the patient had not been monitored at the 24-hour or 72-hour mark (monitoring started too late or was terminated before the time-point), 2) data were missing, 3) the patient died before the selected time-point, 4) the $PbtO_2$ catheter had been misplaced, i.e. not in white matter (as viewed on head CT scan), or 5) the $PbtO_2$ monitor malfunctioned.

Statistical analysis

Means and standard deviations or medians and interquartile ranges (IQR) are reported based on normality of data distribution. Significance was set at p=0.05. $PbtO_2$ at 24 hours post-injury was compared with $PbtO_2$ at 72 hours hours post-injury. In addition, the full first 24 hours of monitoring were compared with the 24 hours of monitoring surrounding the 72-hour mark. The $PbtO_2$ / FiO_2 ratio was similarly compared. Finally a generalized estimating equation was used to compare these values while accounting for inter-individual differences between patients.

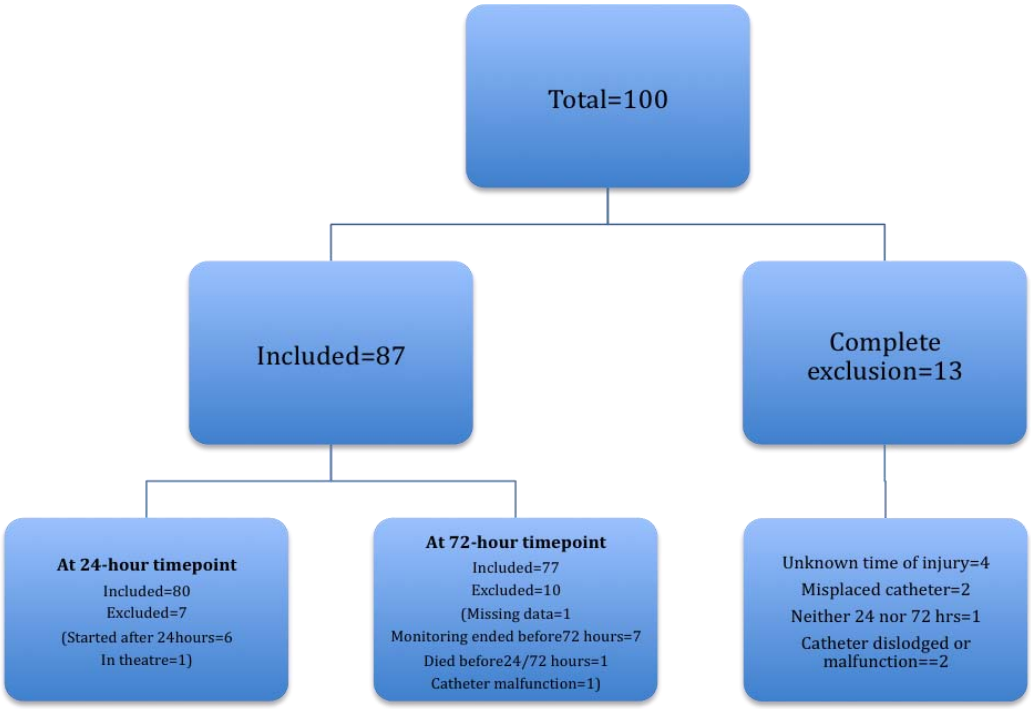
Results

A total of 100 children less than 14 years old with severe TBI, were admitted to the pediatric ICU and underwent $PbtO_2$ monitoring between June 2006 and January 2010. Overall, $PbtO_2$ was monitored for 11,700 hours in 100 patients. Thirteen patients were completely excluded for the following reasons: 1) Unknown time of injury (4), 2) Misplaced catheter (2), 3) Neither 24/ nor 72 hour data (1), 4) Died before 24 hours (4), 5) Catheter dislodged/malfunction (2). This left 87 patients for analysis (Figure 1).

Of these, 7 patients were excluded from the 24 hour time-point for the following reasons: 1) Monitoring started after 24 hours (6), 2) Patient in the operating room at the 24 hour mark (1). Therefore, 80 patients were left for examination at the 24 hour time-point.

For the 72 hour time-point, 10 patients were excluded from analysis for the following reasons: 1) Missing data (1), 2) Monitoring ended before 72 hours (7), 3) Died before 72 hours (1), 4) Catheter dislodged or malfunction (1).

Figure 1. Patient inclusion and exclusion.



General results

The age distribution of patients in this study was: < 2years (n=15, 15%), 2-6 years (n=41, 41%), 7-10 years (n=28, 28%), and 11-15 years (n=16, 16%). There were 67 males and 33 females. Road traffic incidents were the most common cause of injury (79%) and 61% sustained polytrauma. Median GCS before monitoring was 6 (range 3-8), median motor response was 4 (range 1-5). General demographic data are shown in (Table 1).

Table 1. General demographic data.

Age	**Number**
<2 years	15
2-6 years	41
7-10 years	28
11-15 years	16
Gender	
Male	67
Female	33
Mechanism of injury	
Blunt assault	2
Crush injury	4
Fall from height	4
Penetrating head injury	6
Motor vehicle accident	81
Non-accidental injury	3

The average duration of monitoring was 5.8 ± 3.2 days (range 1-15 days), and on average patients stayed in the ICU for 8 ± 4.2 days (range 1-21 days). Apart from poor placement of $PbtO_2$ probes there were no complications associated with any of the $PbtO_2$ monitors.

Summary of general physiological data

Mean $PbtO_2$ for pooled data for the duration of monitoring was 32.8 ± 12.9 mmHg (range 0-98.9). The day of lowest mean $PbtO_2$ (for pooled data) was day 1 (mean $PbtO_2$ 24.6 mmHg) and the day of highest $PbtO_2$ was day 6 (mean $PbtO_2$ 34.8 mmHg). Mean ICP and CPP were 14±6.7 mmHg and 67±14mmHg respectively. Respiratory indices were as follows: mean ventilator FiO_2 49±17, mean arterial partial pressure of oxygen 19.5±10kPa, and mean arterial partial pressure of carbon

dioxide 4.7±1.1kPa. Hemoglobin was 10.8±1.7g/dl and mean serum sodium was 143±5.8mmol/L (Table 2).

Table 2. General physiological data over full duration of monitoring.

Physiological parameter	Range	Q1	Mean	Median	Q3	Standard deviation
$PbtO_2$	0-98.9	23.8	32.77	31.2	39.9	12.87
MAP	30-125	73	81.6	81	90	13.10
ICP	0-76	10	14.52	14	18	6.7
CPP	2-124	58	67.12	67	76	14.44
FiO_2	10-100	40	48.95	45	60	17.16
PaO_2(ABG) (kPa)	4.28-78.1	12.2	19.58	17.5	24.7	10.03
pCO_2 (kPa)	1.8-13.5	3.91	4.66	4.6	5.24	1.12
Hemoglobin	5.6-17	9.6	10.77	10.6	11.9	1.72

Q1= first quartile, Q3=third quartile, $PbtO_2$=brain oxygen tension, MAP=mean arterial pressure, ICP=intracranial pressure, CPP=cerebral perfusion pressure, FiO_2=inspired fraction of oxygen, PaO_2=partial pressure of oxygen, pCO_2=partial pressure of carbon dioxide

Analysis of selected time-points

Summary values: Mean $PbtO_2$ was 25.8±13.3 mmHg at the 24-hour post-injury mark (early), and 33.9±12.7 mmHg at 72 hours post-injury (late). For the whole first 24 hours of monitoring and the 24-hour period around the 72-hour mark, mean $PbtO_2$ was 27.4±11.7 mmHg and 33.0±12.0 mmHg respectively. The ratio of $PbtO_2$ / FiO_2 for the first 24 hours was 0.60±0.33, and for the later period was 0.79±0.41. When we compared the results of the early and late periods for patients who had data at both time points, $PbtO_2$ at 24 hours was significantly less than $PbtO_2$ at 72 hours (p<0.001). The mean difference was 7.98 mmHg (95% confidence interval 4.32 to 11.65), or 31% higher at the later time-point compared to baseline. Using a generalized estimating

equation to account for inter-individual differences, the results at the earlier period were also significantly less than the later period for all parameters examined, i.e. $PbtO_2$ during the first 24 hours versus at the 72-hour mark (p<0.001, mean difference 6.42mmHg), and the $PbtO_2$ / FiO_2 ratio in the first 24 hours versus the 24 hours around the 72 hour mark (p<0.001, 34% higher at the later time-point) (Table 3).

Table 3. Physiological data at 24 hour time point.

Physiological parameter	Range	Q1	Mean	Median	Q3	Standard deviation
$PbtO_2$	1.3-91.6	16.9	25.77	25.1	33.7	13.3
MAP	47-110	71	78.09	75	86	12.31
ICP	1-66	10	15.86	15	19	9.09
CPP	27-95	53	62.10	61	68	13.50
FiO_2	21-93	40	51.53	50	60	16.23
PaO_2 (ABG) (kPa)	10-37.9	23	25.44	25.8	28.95	7.39
pCO_2 (kPa)	2.6-6.19	3.41	4.12	4.1	4.78	0.92
Hemoglobin	9.4-11.6	9.4	10	9.5	10.1	1.07
Temperature	35.4-39.3	36.72	37.21	37.2	37.6	0.81
Sodium	131-155	139.5	142.91	142.5	145.75	6.18

Q1= first quartile, Q3=third quartile, $PbtO_2$=brain oxygen tension, MAP=mean arterial pressure, ICP=intracranial pressure, CPP=cerebral perfusion pressure, FiO_2=inspired fraction of oxygen, PaO_2=partial pressure of oxygen, pCO_2=partial pressure of carbon dioxide

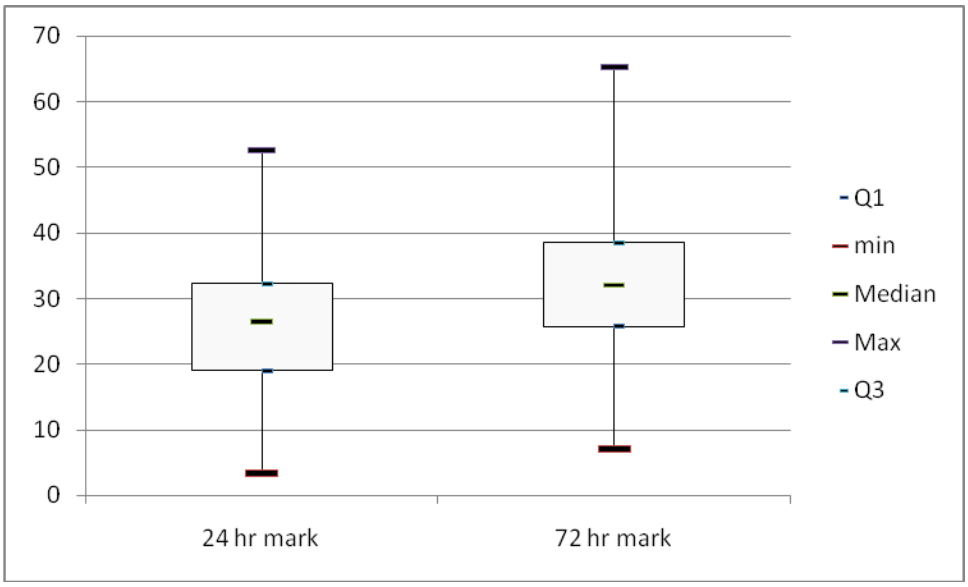
Table 4. Physiological data at 72 hour time point.

Physiological parameter	Range	Q1	Mean	Median	Q3	Standard deviation
$PbtO_2$	15.9-68.6	24.37	33.95	32.1	42.92	12.71
MAP	55-109	72	80.88	80.5	89	11.92
ICP	1-44	10	14.3	13	18	7.09
CPP	41-100	56	66.68	67	74.5	13.47
FiO_2	21-50	40	46.72	40	50	16.15
PaO_2 (ABG) (kPa)	8.8-34	10.7	16.88	12.1	24.4	7.92
pCO_2 (kPa)	3.63-7.07	4.12	4.85	4.93	5.35	0.97
Hemoglobin	8.4-13.3	9.7	10.92	10.4	12.25	1.62
Temperature	34.6-39.5	36.5	36.87	37	37.35	0.88
Sodium	141-149	143	144.7	144	146.5	2.75

Q1= first quartile, Q3=third quartile, $PbtO_2$=brain oxygen tension, MAP=mean arterial pressure, ICP=intracranial pressure, CPP=cerebral perfusion pressure, FiO_2=inspired fraction of oxygen, PaO_2=partial pressure of oxygen, pCO_2=partial pressure of carbon dioxide

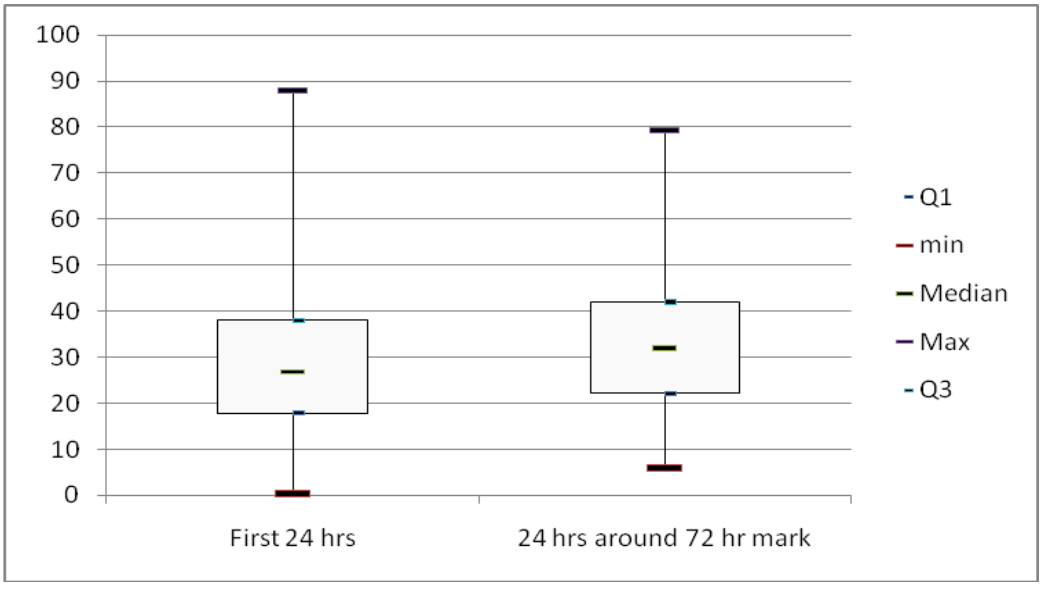
Frequency of low $PbtO_2$: At the 24 hour mark, $PbtO_2$ was <10mmHg in 8 patients (10% of the patients examined at the 24 hour mark) and <5mmHg in 3 (3.8%). Two of these patients were hemodynamically unstable at the time. At the 72 hour mark, none of the patients had a $PbtO_2$ <10mmHg, and only 7 patients had $PbtO_2$ <20mmHg (Table 5)

Figure 2. Individual timepoints – 24 hour mark and 72 hour mark.



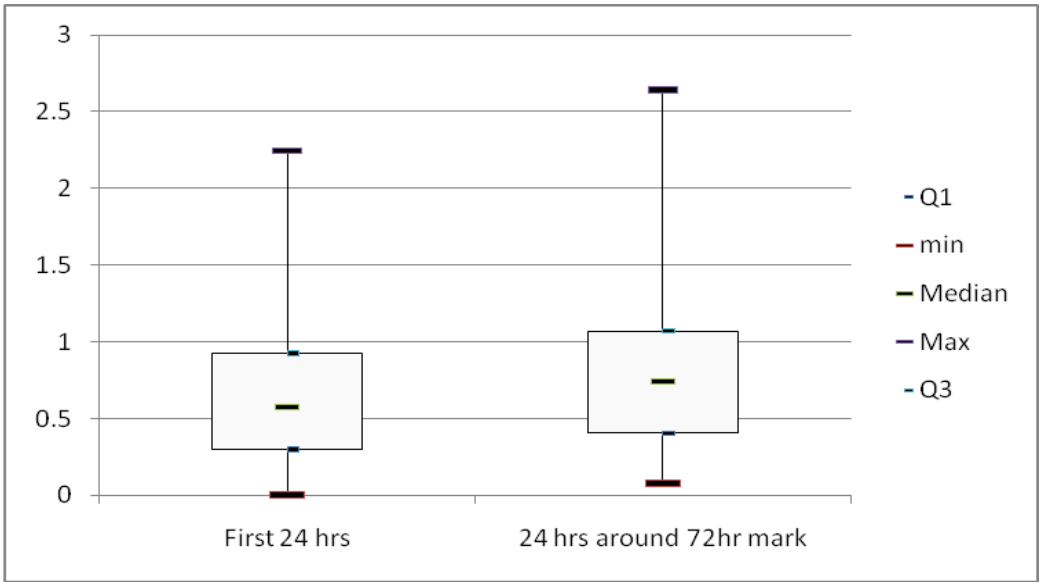
Q1=first quartile, min=minimum, Q3=third quartile, max=maximum

Figure 3. Initial 24 hour period compared to 24 hour period around 72 hour mark.



Q1=first quartile, min=minimum, Q3=third quartile, max=maximum

Figure 4. Comparison of FiO_2 / $PbtO_2$ ratio – initial 24 hour period vs. 24 hour period around 72 hour mark.



Q1=first quartile, min=minimum, Q3=third quartile, max=maximum

Table 5. Episodes of low $PbtO_2$ at 24-hour time point.

At 24 hours	**$PbtO_2$ <20**	**$PbtO_2$ <15**	**$PbtO_2$<10**	**$PbtO_2$ <5**
N=80	25	12	8	3
Percentage (%)	31.25	15	10	3.75

Table 6. Episodes of low $PbtO_2$ at 72-hour time point.

At 72 hours	**$PbtO_2$ <20**	**$PbtO_2$ <15**	**$PbtO_2$ <10**	**$PbtO_2$ <5**
N=77	7	0	0	0
Percentage (%)	9.09	0	0	0

When examined over the full course of monitoring, episodes of $PbtO_2$ <20mmHg occurred in 77 of 87 patients (88%), <10mmHg in 47 patients (54%) and <5mmHg in 18 (21%).

Table 7. Episodes of low $PbtO_2$ over the whole course of monitoring.

Whole duration of monitoring	**$PbtO_2$<20**	**$PbtO_2$<15**	**$PbtO_2$<10**	**$PbtO_2$<5**
N=87	77	63	47	18
Percentage (%)	88.50	72.41	54.02	20.68

Discussion

The occurrence of cerebral ischemia in the pathophysiology following severe TBI is well established (121, 22, 124), but the frequency is often debated. As discussed earlier, postmortem studies suggest a high incidence of PTCI (13, 14, 22), but antemortem detection of early ischemia has remained difficult to demonstrate, despite numerous attempts using various modalities (11, 12, 15, 142, 149, 159). The difficulty in conclusively demonstrating this elusive entity lies largely in the discordance regarding the definition of ischemia and the limited spatial and temporal resolution of the various modalities employed. Therefore, comparison between studies is difficult and the treating clinician is left wondering about the true risk of ischemia in patients with acute severe TBI.

The difficulty in reaching a widely accepted definition of ischemia arises because of several reasons. Earlier studies examining CBF in experimental and clinical environments described ischemia in terms of CBF thresholds i.e. less than 18ml/100g/min (157, 158, 159). However, this does not take into account the issue of coupling between metabolism and CBF. In some patients, low CBF may be appropriately coupled with reduced metabolism. On the other hand, relatively

'normal' CBF may be inappropriately low in the presence of increased metabolic demand. More recently, studies in TBI have evaluated not only CBF, but also OEF, $AVDO_2$, $PbtO_2$, CvO_2, $SjvO_2$ and lactate/pyruvate ratio (81, 129, 11, 78, 67, 17, 27). The various modalities employed, and their benefits and limitations in the management of TBI patients, have been discussed in chapter 3. None of these modalities provides a complete picture of the problem of ischemia in TBI. Imaging modalities such as PET have increased specificity for diagnosing ischemia, but it may not be possible to extrapolate these results to the full period during which patients are potentially at risk of ischemia, and in particular unstable patients, because of its limited temporal resolution and dependence on relatively stable patients that can be moved out of the ICU. Methods employed in the neurocritical care unit as monitors of brain oxygenation or metabolism have increased sensitivity for detecting adverse events, including ischemia, over the full duration of monitoring, but lack specificity for the diagnosis of ischemia because several factors influence their readings.

$PbtO_2$ as a monitor for ischemia and tissue hypoxia has specific limitations. First it is a focal monitor, therefore it reflects accurately only tissue that is being monitored. However, it appears that monitoring in 'uninjured white matter' in a diffusely injured brain may reflect global changes in the rest of the brain (74). Second, several factors influence $PbtO_2$, therefore it is not an ischemia monitor per se. However, experimental and clinical data demonstrate a consistent decrease in $PbtO_2$ when CBF is reduced (67, 141, 148, 150, 156), therefore it is likely that when ischemia occurs (and affects the area being monitored, as in a global insult), $PbtO_2$ is likely to be reduced. However, it must be remembered that several other factors may also lead to a decrease in $PbtO_2$.

The identification of cerebral ischemia remains an appealing quest, as there may well be an element of reversibility to the compromised tissue if it is detected early. The window of opportunity to intervene, however, is short before the damage incurred becomes permanent. This justifies the resources expended by numerous investigators aiming to quantify the burden of ischemia.

Comparison of results

The results from this study show a relatively low prevalence of low brain tissue oxygen at the selected timepoints, as defined by $PbtO_2$ <10mmHg, which may be due to ischemia or other causes of tissue hypoxia. As expected, $PbtO_2$ early after injury is lower than at a later time point. Mean values on day 2 were 31-36% higher than the corresponding values in the first 24 hours. This is consistent with other publications reporting lower values for $PbtO_2$ and CBF early in the post-injury phase and a higher frequency of cerebral ischemia or hypoxia. The differences are slightly less when one examines a longer period of time, rather than a single 24 or 72 hour time-point, as was done here with the first 24 hours compared with the 24 hour period surrounding the 72-hour mark, likely because a longer period dilutes some of the differences that occur over time. Arguably, if an earlier time point was selected, say 6-12 hours after injury, the frequency of low $PbtO_2$ may have been higher. At hour 24 after injury, $PbtO_2$ was <10mmHg in 10% of patients, while at the 72 hour mark, no patient had $PbtO_2$ <10mmHg. On the other hand, when the full duration of monitoring was examined, as many as 88% of patients had episodes of $PbtO_2$ <20mmHg, 54% had episodes <10mmHg, and 21% had episodes <5mmHg. These results are consistent with the known dynamic nature of TBI. Each of these episodes is potentially clinically significant, even though they may be temporary. However, they may occur at unpredictable times after TBI is sustained. These results support the concept that the timing of the study after TBI substantially affects the findings, i.e. studies early after TBI are likely to detect more adverse events, but also that regardless of the timing of the study, caution must be exercised when interpreting the findings of a study that is limited to a single point in time in a head-injured patient. Given that there is no perfect monitor that has both good spatial and temporal resolution, this would suggest that the burden of cerebral ischemia, or other adverse events post-TBI, should be best interpreted using data from both static imaging technologies and dynamic, continuous monitors in the ICU.

Methodological limitations

There are several potential limitations to this study. First, as discussed above, a $PbtO_2$ monitor is not an ischemia monitor per se. Several factors influence $PbtO_2$, in particular arterial partial pressure of oxygen. However, reduced $PbtO_2$ is likely to be clinically significant, regardless of the cause. Reduced CBF is one of the important causes for low $PbtO_2$, and $PbtO_2$ consistently decreases when CBF is reduced experimentally. Reduced $PbtO_2$ is associated with poor outcome in adults and children and so likely represents a clinically important adverse event. It is possible that the combination of $PbtO_2$ with a complimentary modality, such as micodialysis (MD) or CBF may yield a more specific estimate of ischemia. Second, $PbtO_2$ is a focal measure of tissue oxygenation and may miss ischemic/hypoxic events occurring elsewhere in the brain. Therefore, current data may underestimate the true frequency of reduced tissue oxygenation. Third, the patient sample is a pediatric cohort of patients whereas the data from most of the studies discussed in this work involve adult patients and these may not be completely comparable. Therefore, the results of this study require validation in an adult cohort. However, the frequency of reduced $PbtO_2$ between adults and children appears to be similar, and low $PbtO_2$ is independently associated with poor outcome in both. Moreover, this study emphasizes the principles of comparing frequencies at single time points and over the full duration of monitoring, rather than specific values, so it is not unreasonable to generalize these results. Fourth, the $PbtO_2$ threshold of 10 mmHg may not be the most appropriate threshold for detecting ischemia or critical tissue hypoxia. Some authors suggest a lower threshold of 6-8 mmHg. On the other hand, most centres treat $PbtO_2$ when it is reduced below 20mmHg. Much work still needs to be done to better understand the association between $PbtO_2$ thresholds and ischemia/critical tissue metabolic events. Still, regardless of the threshold chosen, the principle of comparing one threshold at different time-points, should be similar at different $PbtO_2$ thresholds. $PbtO_2$ less than 10mmHg has a strong association with outcome in pediatric and adult TBI (17, 67, 74, 75, 76, 263) and experimentally, $PbtO_2$ less than 10 mmHg also corresponds with classic measures of tissue ischemia (41, 129, 148, 150, 154, 171, 215, 263). Fifth, the study employs a single modality of monitoring, the

results of which cannot necessarily be generalized. However, the principle of the differences inherent in comparing single point-in-time data with data collected continuously over a long period should apply to all modalities used to measure adverse events occurring after TBI.

It is clear that much work still needs to be done to assess the true risk of cerebral ischemia in patients with TBI, and more importantly whether this ischemia can be effectively reversed to improve outcome. At present, the frequency is debated. This is an important issue, because if cerebral ischemia is a relatively common event causing secondary injury, then this should direct treatment protocols. Improved outcomes seen in both adult and pediatric TBI patients, using treatment strategies aimed at the maintenance of adequate oxygenation and perfusion are well documented (77, 176, 178, 179), however, it is difficult to demonstrate conclusively that secondary ischemic events are being effectively detected and treated, and that this leads to better outcome. More specific data on which elements of these strategies are effective, especially with respect to the prevention of brain ischemia, would better inform global strategies to improve outcome after TBI. Without these data, clinical care is likely to continue with some uncertainty as all therapies to reduce the risk of brain ischemia or tissue hypoxia, such as increased CPP and normobaric hyperoxia, have potential risks when applied uniformly to all patients. Selecting which patients are at particular risk of developing ischemia or tissue hypoxic events, may allow aggressive targeted therapy to patients who stand to gain the most from this approach.

Conclusion

Although cerebral ischemia is thought to be an important factor causing secondary injury in TBI, current evidence does not clarify what the burden of ischemia in TBI truly is because of the complexity of its diagnosis. Although imaging techniques such as PET are superior in terms of spatial resolution and the indices of metabolism that can be measured, the results of this study suggest that selection of individual

time-points for examination, especially for stable patients, may significantly underestimate the overall frequency of adverse cerebral events after TBI.

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