The Effects of Whole Body Cooling Following Traumatic Brain Injury

A thesis submitted to the University of Manchester for the degree of Doctor of Medicine in the faculty of Medical and Human Sciences

2011

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Brain Injury Research Group
School of Biomedicine
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Abstract

Abstract of thesis submitted by Miss Nicola Jayne Johnston to The University of Manchester for the degree of Doctor of Medicine entitled:

The Effects of Whole Body Cooling Following Traumatic Brain Injury

Submitted September 2010

Introduction: Prevention of secondary brain injury is key in the management of severe traumatic brain injury in intensive care. A raised temperature post traumatic brain injury is considered by many to be a potential insult, although the evidence from animal and human studies is ambiguous. Due to lack of evidence for induced hypothermia, the aim of current clinical temperature management following severe traumatic brain injury is often the ‘middle ground’ or maintained normothermia. In our intensive care unit a step wise cooling protocol is initiated in the event of a rise in temperature. Preliminary work from our unit suggested that reduction of measured temperature during cooling is variable, and may be associated with changes in physiological parameters. In order to investigate this further, we carried out a detailed observational study to observe the effects of whole body cooling on brain temperature and on certain physiological and biochemical parameters. The aim was to observe for any effects of cooling that could contribute to secondary injury. In addition, we undertook a patient review to examine for possible relationships between raised temperature, the length of time temperature was raised, and clinical outcome, in a larger set of patients. These two studies, the patient review and observational study, constitute the work performed for this thesis.

Methods: Patient Review – All patients admitted following a severe traumatic brain injury over a 12 month period were eligible for inclusion in the study. The case notes of each patient were reviewed and assessed at three time points. At admission the initial temperature reading was noted. At the other two time points patients were only included if they remained on ICU. Peak temperature and the length of time temperature was raised were noted. Analysis was performed using logistic regression to look for a relationship with outcome.

Observational study – This more detailed study took place over the same time period and involved a small cohort of patients with brain temperature monitoring who did not require immediate surgical intervention. A maximum of two cooling episodes were studied in each recruited patient. Changes in brain temperature, ICP, CPP, S100b, IL-6 and TNF-α were monitored during the recruitment period and more frequently during studied cooling episodes. In addition BIS monitoring was performed during studied cooling episodes.

Results: Patient review – There was no evidence in our population of patients that a raised temperature or the length of time a temperature was raised was associated with an increased risk of death.

Observational study – All methods of temperature reduction were observed to be poorly effective at reducing brain temperature. There were observed changes in the monitored physiological and biochemical parameters that may have been directly related to the cooling process and may be clinically significant.

Discussion – Further laboratory and clinical studies are required to unlock the enigma of brain temperature management following severe traumatic brain injury. Further studies into the use of surface cooling and gastric lavage should be undertaken to fully assess their potential risks and benefits. In the United Kingdom and Ireland there is a need for a consensual approach to temperature management.
Declaration

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Special thanks to Timothy Rainey for his assistance throughout the project and to Dr Roy Sherwood for performing the analysis on our serum samples. Many thanks to Andy Vail for his invaluable statistics input.

Dedication

This work is dedicated to my kind and patient husband and my wonderful daughter.

John and Naoimh
## Abbreviations

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<th>Description</th>
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<tbody>
<tr>
<td>A&amp;E</td>
<td>Accident and Emergency</td>
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<tr>
<td>AIS</td>
<td>Abbreviated Injury Score</td>
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<td>BBB</td>
<td>Blood-Brain Barrier</td>
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<td>BIS</td>
<td>Bispectral Index</td>
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<td>BTF</td>
<td>Brain Trauma Foundation</td>
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<tr>
<td>Ca^{2+}</td>
<td>Calcium</td>
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<tr>
<td>CBF</td>
<td>Cerebral Blood flow</td>
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<td>CK-BB</td>
<td>Creatine Kinase Isoenzyme BB</td>
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<td>CNS</td>
<td>Central Nervous System</td>
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<td>Cerebrospinal Fluid</td>
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<td>Computed Tomography</td>
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<td>Coefficient of Variation</td>
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<td>Diffuse Axonal Injury</td>
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<td>EAAs</td>
<td>Excitatory Amino Acids</td>
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<td>Electroencephalograph</td>
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<td>Enzyme Linked Immunoassay</td>
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<td>EMG</td>
<td>Electromyogram</td>
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<td>Glasgow Coma Scale</td>
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<td>GFAP</td>
<td>Glial Fibrillary Acidic Protein</td>
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<td>GMNC</td>
<td>Greater Manchester Neurosciences Centre</td>
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<td>H_{2}O_{2}</td>
<td>Hydrogen Peroxide</td>
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<td>HDU</td>
<td>High Dependency Unit</td>
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<td>Middle Cerebral Artery</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>Na⁺</td>
<td>Sodium</td>
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<td>NADP</td>
<td>Nicotinamide Adenine Dinucleotide</td>
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<td>NADPH</td>
<td>Nicotinamide Adenine Dinucleotide Phosphate</td>
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<td>NICE</td>
<td>National Institute for Clinical Excellence</td>
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<td>NMB</td>
<td>Neuromuscular Blockade</td>
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<td>NO</td>
<td>Nitrous Oxide</td>
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<td>NSE</td>
<td>Neurone Specific Enolase</td>
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<td>PTV</td>
<td>Post Traumatic Cerebral Artery Vasospasm</td>
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<td>Relative Light Units</td>
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<td>Reactive Oxygen Species</td>
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<td>Ramsay Sedation Score</td>
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<td>RTA</td>
<td>Road Traffic Accident</td>
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<td>SAH</td>
<td>Subarachnoid Haemorrhage</td>
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<td>SAS</td>
<td>Sedation-Agitation Scale</td>
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<td>SBDPs</td>
<td>Spectrin and its Breakdown Products</td>
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<td>Standard Deviation</td>
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<td>SRFT</td>
<td>Salford Royal Foundation Trust</td>
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<td>TARN</td>
<td>Trauma Audit and Research Network</td>
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<td>T&lt;sub&gt;brain&lt;/sub&gt;</td>
<td>Brain Temperature</td>
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<td>TCD</td>
<td>Transcranial Doppler</td>
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<td>TCDB</td>
<td>Trauma Coma Data Bank</td>
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<td>TNF-α</td>
<td>Tumour Necrosis Factor-α</td>
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<td>Rectal Temperature</td>
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<td>tSAH</td>
<td>Traumatic Subarachnoid Haemorrhage</td>
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<td>TBI</td>
<td>Traumatic Brain Injury</td>
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<tr>
<td>UCH-L1</td>
<td>Ubiquitin C-terminal hydrolase</td>
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<td>United Kingdom</td>
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Chapter 1

Introduction
This chapter introduces traumatic brain injury (TBI) and the complex problem of secondary brain injury and insults. A raised temperature following TBI is considered by some to be a potential secondary injury while others consider induced hypothermia to be a potential neuroprotectant. This chapter discusses the evidence and controversies surrounding temperature and temperature management in patients following a severe TBI. It also introduces the two separate but linked studies of patients with a severe TBI that form this thesis. The first study is a patient review and the second is an observational study.

1.1 Clinical

1.1.1 The Burden of Traumatic Brain Injury

TBI is often thought of as a ‘silent epidemic’. Worldwide, approximately 10 million people experience a severe head injury (HI) every year (Langlois, Rutland-Brown, and Wald 2006). It accounts for up to half of all deaths and for most cases of permanent disability following trauma (Jennett 1996).

HI is often used synonymously with TBI, although they describe slightly different injuries. HI is a general term used to describe injuries of all severities to the scalp, skull and brain. TBI is a more specific term used to describe injury to the brain only. It is defined as a non-degenerative, non-congenital insult to the brain from an external mechanical force, which can lead to permanent or temporary impairment of cognitive, physical and psychosocial functions with an associated diminished or altered state of consciousness (www.emedicine.com). Not all patients who sustain a HI also sustain a TBI.

Epidemiology of TBI

Epidemiological data of TBI is important to ensure that appropriate preventative measures can be initiated and that necessary services are available at all stages for the care of patients
with TBI. This data is achieved by examining admission rates, incidence, disability and prevalence and mortality.

Establishing reliable local admission statistics can be difficult for a variety of reasons, such as inaccuracies of admission data. Admission data is based on the classification of patients according to the International Classification of Diseases (ICD) 10 codes (www.who.int). One published report suggests that by using ICD-10 codes, less than 50% of all HI’s may be detected (Deb 1999). One possible explanation for this is that coding is often left to junior doctors and non-medical clinical staff who may not be fully aware of the precise definitions. Using ICD-10 codes also makes it difficult to differentiate between HI and TBI and most admission figures are available for HI. Admission data has another drawback in that it does not take into account those who did not attend Accident and Emergency (A&E). In the United Kingdom (UK) more than one million people attend A&E per year with a HI (Select Committee on Health Third Report; Head Injury: Rehabilitation, 2001). The regional range of admissions is 210-404 per 100 000. In other developed countries this range is 93-410 per 100 000 (Jennett 1996). Comparison of admission rates can be difficult due to local and national admission policies.

Data from the Salford Royal Foundation Trust (SRFT) collected over a 12-month period (2004-2005) revealed that there were 726 patients admitted with HI (ICD-10 codes S00-09) from A&E, of which 64 were admitted under the care of the neurosurgeons. A further 188 patients were transferred from regional district general hospitals for emergency neurosurgical input (A&E and ICU audit data, unpublished). Additional data from the Trauma Audit and Research Network (TARN) is available from participating hospitals in the North West Region of England (www.tarn.ac.uk).

Since their report in 1988 the British Society of Rehabilitation Medicine indicates that the incidence of HI has changed little (British Society of Rehabilitation Medicine - Rehabilitation
after traumatic brain injury, July 1988; Select Committee on Health Third Report – Head injury: Rehabilitation, April 2001). It reported an incidence of 300 per 100,000. This was divided up into an annual rate of 8 per 100,000 for severe HI, 18 per 100,000 for moderate HI and 250-300 per 100,000 for mild HI. Assuming a UK population of 60 million, this makes for a national incidence, for hospital admission, of 180,000 per year.

The incidence of HI is higher in males, the young and elderly, the unemployed and in urban areas (Tennant 2005). In the male 15 to 60 age group, HI incidence is about twice that of females. The peak incidence in males is between the ages of 15 and 30 years (Jennett 1996).

A significant proportion of survivors of HI are left with disability that can be both considerable and prolonged. Even patients with a mild HI can be left with varying degrees of disability for some months. In the UK it is estimated that 100-150 people per 100,000 are disabled survivors of HI (Select committee on Health Third Report – Head Injury: Rehabilitation, April 2001).

In western countries injury is the leading cause of death under the age of 45 years. In the UK in 1994 the death rate from HI was estimated to be approximately seven per 100,000 (Jennett 1996). In other developed countries such as the United States of America, Australia, Spain and France, mortality of up to two to three times that of the UK has been reported. This is thought, in part, to be due to the fact that road traffic accident deaths are twice as frequent in these countries when compared with the UK (Jennett 1998).

It is clear from the figures demonstrated that TBI impacts greatly not only on health care provision, but also on the individuals who have suffered trauma and their families who continue to live with the consequences of TBI.
1.1.2 Classification of Traumatic Brain Injury

TBI is a heterogeneous disease encompassing a wide range of pathologies and severities. The classification of TBI severity early following injury is essential for a number of reasons. Firstly, the initial severity of TBI will determine the level of care and facilities a patient will require. Secondly, initial severity classification is a major prognostic factor used in the consideration of predicted outcome. The most commonly used initial classification system in clinical practice is the Glasgow Coma Scale (GCS). TBI can also be classified according to morphological criteria based on computed tomographic imaging (CT) or magnetic resonance imaging (MRI). CT examination remains the investigation of choice in the acute phase. It has been postulated that the development of biochemical markers of brain injury might further assist in severity classification.

Glasgow Coma Scale

In severe cases of TBI, the severity is clinically evidenced by the degree and duration of a depressed level of consciousness (van Baalen et al. 2003). The GCS was devised in 1974 as a standardised method of evaluating the level of consciousness in patients with acute neurological disorders (Teasdale and Jennett 1974). It has been shown to have both a high inter and intra-user reliability, and as a result is used widely for initial TBI severity classification (Zasler 1997). Its ease of use also ensures accurate communication of a patient’s level of consciousness between medical staff and accurate evaluation throughout the course of their management. The National Institute for Clinical Excellence (NICE) recommend the use of GCS in the assessment and classification of patients who have sustained a TBI (www.nice.org.uk).
The GCS is based on three response scores. A fully conscious patient will have a GCS score of 15, while the lowest GCS score possible is three (Appendix A). Using GCS, the severity of TBI is often described as mild (14-15), moderate (9-13) or severe (3-8).

The initial GCS score has been shown to correlate highly with acute morbidity and mortality, but less strongly with long-term functional outcome (van Baalen et al. 2003). Long-term functional outcome has shown better correlation with GCS collected at 48-72 hours following injury compared with GCS collected within the first 48 hours following injury (Zasler 1997).

There continues to be much debate as to which GCS score should be recorded for research purposes – best/worst pre-resuscitation or best/worst post-resuscitation scores (Zasler 1997).

For the purpose of this study the worst pre-resuscitation GCS score was documented.

**Radiological Classification**

CT scanning remains the investigation of choice following TBI. In 1992 Marshall and colleagues proposed a CT classification for grouping patients with TBI according to multiple CT characteristics (Marshall et al. 1992). It differentiates between patients with and without mass lesions and permits further discrimination of patients with diffuse injuries into four categories, taking into account signs of raised ICP.

The Marshall classification was devised following analysis of the Traumatic Coma Data Bank (TCDB). It has become widely accepted for descriptive purposes and good interobserver reproducibility between neuroradiologists and neurosurgeons has been demonstrated (Chun et al. 2010). Although there have been studies to support its use as a predictor of outcome, other studies have shown better discrimination by making fuller use of the individual characteristics underlying the Marshall CT classification (Maas et al. 2005; Wardlaw, Easton, and Statham 2002). One study suggests that CT models for predicting outcome could be improved with the addition of the following characteristics – status of basal cisterns, mid-line shift, traumatic subarachnoid haemorrhage (tSAH) and/or intra-ventricular
haemorrhage and differentiation between extradural haematoma versus intradural lesions (Maas et al. 2005). A criticism of the Marshall classification is that it requires knowledge of the post-injury course of the patient and therefore needs to be applied retrospectively rather than prospectively, and that this reflects a clinical decision rather than a CT parameter (Maas et al. 2005; Wardlaw, Easton, and Statham 2002). A further potential criticism is that, particularly in the patients classified as having a diffuse axonal injury, repeat CT scans can show evolution and as a result prognosis will worsen in comparison to the original scan (Servadei et al. 2000). As a result the initial CT may not always be the best predictor of outcome. Formal radiological classification of the initial CT scan using the Marshall classification is rarely used in daily practice in our institution.

Biochemical Classification

Despite the clinical and radiological classification tools available the ability to predict outcome remains difficult. In severe TBI, despite knowledge of GCS and CT findings, it can be difficult to differentiate patients who will have a favourable or unfavourable outcome. Even in mild TBI, clinical and radiological classifications do not always identify those who will require follow-up due to disability. As a result, there has been considerable interest in the development and use of biochemical markers as tools to assist in the classification of brain injury severity. Several such markers have been proposed, such as the cytoplasmic enzyme lactic dehydrogenase (LDH) and creatine kinase isoenzyme BB (CK-BB). However, both were shown to have a lack of specificity for brain tissue (Bakay and A A Ward 1983; D N Carney et al. 1984; Yoneyama et al. 1992). Neurone specific enolase (NSE) was also investigated but found to be present in red blood cells and levels following TBI were confounded by haemolysis (Beaudeux et al. 2000). Other new markers such as glial fibrillary acidic protein (GFAP), spectrin and its breakdown products (SBDPs) and Ubiquitin C-terminal hydrolase (UCH-L1) continue to be investigated (Kövesdi et al. 2010; Papa et al.
Currently, the brain biomarker S100b, which is highly specific for lesions of the CNS, has been the most consistent marker of brain injury and outcome following TBI (Kővesdi et al. 2010) (See 1.5.3).

1.1.3 Traumatic Brain Injury

The mechanical deformation of the brain that occurs at the moment of impact in TBI results in primary brain injury. It leads to focal injuries, such as contusions and cortical lacerations and diffuse axonal injury (DAI). The brain injury sustained at the time of impact is irreversible and cannot be modified.

Following TBI numerous pathways are set into motion, which can result in further injury to the brain in the hours and days following the initial insult. This is known as secondary brain injury and, unlike primary brain injury, has the potential to be modified.

1.1.4 Secondary Brain Injury Pathways

Inflammation

The central nervous system (CNS) has historically been defined as an ‘immunologically privileged organ’ due to its tight separation from the peripheral circulation by the blood-brain barrier (BBB). In more recent times it has become evident that the CNS is a rich source of inflammatory mediators. Astrocytes, microglia and neurones have been shown to be capable of producing immune mediators including cytokines, chemokines and complement activation proteins and to express the receptors for these immune mediators (Rothwell and Hopkins 1995; Morgan and Gasque 1996; Ransohoff 2002). A potent immune response can be induced within injured brain.

A. Cytokines
Cytokines are a diverse group of low-molecular weight polypeptides. They act primarily as mediators of inflammation, both pro- and anti-inflammatory. They also stimulate the formation and release of many other secondary mediators such as free radicals, neuropeptides and arachidonic derivatives, and up regulation of the activity of adhesion molecules. Laboratory and human studies have shown that there are at least three important cytokines released following head injury: tumour necrosis factor α (TNF-α), Interleukin-1β (IL-1β) and Interleukin-6 (IL-6).

Tumour necrosis factor-α (TNF-α)

Due to low levels of TNF-α expression in the healthy brain it has been difficult to determine its precise role in physiological conditions. In experimental models of TBI, TNF-α is up regulated within a few hours after trauma (Fan et al. 1996; Gourin and Shackford 1997; Schmidt et al. 2005). This has been confirmed by clinical studies which have shown a rise in both serum and cerebrospinal fluid (CSF) levels (Goodman et al. 1990; Morganti-Kossman et al. 1997). The magnitude of TNF-α elevation following TBI has been has been shown to be similar to that seen in meningitis, sepsis, cancer and burns (Goodman et al. 1990). TNF-α seems to penetrate CSF from the periphery as well as from intrathecal synthesis. In TBI, TNF-α appears to have a dual role in HI, both beneficial and detrimental. Various experimental studies have documented the detrimental role of TNF-α in the acute phase with regard to neuronal injury and also shown that the presence of TNF-α synergistically enhances the potent neurotoxic effects of IL-1 (Ziebell and Morganti-Kossmann 2010). Furthermore, benefit was achieved following early experimental pharmacological inhibition of TNF-α (Knoblach, Fan, and Faden 1999; Shohami et al. 1996; Shohami et al. 1997). However, this was not translated to the bedside. A randomised control trial in TBI patients demonstrated no difference in outcome at 6 months in patients treated with a
TNF-binding protein when compared to the control group (Maas et al. 2006). In gene knockout mice with a TNF-α deficiency and lack of TNF-α receptors, benefit in the early period after trauma (one to two days) but detriment later in the post-traumatic course (two to four weeks) have also been reported (Knoblach, Fan, and Faden 1999; Morganti-Kossmann et al. 2002; Scherbel et al. 1999; Shohami, Ginis, and Hallenbeck 1999; Sullivan et al. 1999). Thus there is evidence that TNF-α exerts both beneficial and detrimental effects after brain injury due to biphasic early neuroinflammatory and late neuroregenerative mechanisms (Ziebell and Morganti-Kossmann 2010).

Interleukin-1 family (IL-1)
This family comprises of interleukin-1α (IL-1α), interleukin-1β (IL-1β) and interleukin-18 (IL-18). Following HI, both IL-1α and IL-1β gene expression is up regulated within minutes, followed by detectable protein levels within hours of trauma (Gourin and Shackford 1997; Tchelingerian et al. 1993; Vecil et al. 2000; Woodroofe et al. 1991). IL-1 is an important initiator of the immune response, playing a key role in the onset and development of a complex inflammatory cascade (Ziebell and Morganti-Kossmann 2010). The expression of IL-1 has been associated with BBB dysfunction following experimental brain injury in mice (Vecil et al. 2000). Experimental inhibition of IL-1 by administration of IL-1 receptor antagonist (IL-1ra) has been shown to reduce neuronal damage in rodent brain (Toulmond and Rothwell 1995). Further emphasis of the role of IL-1 in the induction of neuroinflammation after TBI was demonstrated experimentally, with improved neurological recovery and delayed pro-inflammatory cytokine induction, in transgenic mice with CNS-specific over expression of soluble IL-1ra (Tehranian et al. 2002). The neurotoxic effects of IL-1 have been shown to be enhanced by the presence of TNF-α, suggesting that these cytokines act in a synergistic fashion (Chao et al. 1995).
**Interleukin-6 (IL-6)**

IL-6 is a cytokine with pleiotropic functions within the CNS (Gadient and Otten 1997). Elevated intracranial and serum IL-6 levels have been found in experimental settings of brain injury (Taupin et al. 1993; Woodroffe et al. 1991). In one animal model of diffuse axonal injury, IL-6 was detectable in rat serum and CSF two hours following injury, reached a peak at four hours and returned to normal by 24 hours (Morganti-Kossman et al. 1997). In patients, elevations have been found in brain parenchyma, CSF and serum in patients with TBI, as early as four to six hours from injury (Hayakata et al. 2004; Kalabalikis et al. 1999; Kossmann et al. 1996; McClain et al. 1991; Singhal et al. 2002; Winter et al. 2004). IL-6 appears to have anti-inflammatory and neuroreparative actions. This is supported by its ability to inhibit TNF-α synthesis, induce nerve growth factor, promote neuronal differentiation and survival and counteract N-methyl-D-aspartate-mediated toxicity (Morganti-Kossmann et al. 2001). Human studies have also suggested that peak CSF and parenchymal concentrations of IL-6 correlate with improved outcome following TBI (McClain et al. 1991; Singhal et al. 2002; Winter et al. 2004). Clinical studies have demonstrated the ability of IL-6 to induce the hepatic acute-phase response after leaking into the peripheral circulation across a defective BBB (Kossmann et al. 1995; McClain et al. 1991).

**B. Complement**

The activation of complement may represent one of the first cascades of neuroinflammation activated after TBI. Neurones, astrocytes, microglia and oligodendroglia are all sources of complement (Schmidt et al. 2005; Morgan and Gasque 1996). The generation of proteolytic complement fragments leads to a wide variety of inflammatory effects, such as opsonisation of pathogens for phagocytosis, induction of increased vascular permeability, recruitment of phagocytic cells, augmentation of the
acute phase response, B-cell activation, and cytolysis of pathogens by membrane pore formation (Schmidt et al. 2005). Clinical and experimental studies have revealed pathophysiological mechanisms of complement-mediated delayed neuronal injury after TBI. These include the recruitment of inflammatory cells into the intrathecal compartment, the induction of BBB dysfunction, induction of neuronal apoptosis and complement-mediated homologous cell lysis (Kilpatrick et al. 2000; Lynch et al. 2004; Singhrao et al. 2000). Early complement-mediated intracranial invasion by neutrophils and later by monocytes/macrophages enhances neuroinflammation due to the release of oxygen radicals, proteases and complement-mediated induction of pro-inflammatory cytokine synthesis (Fischer, Jagels, and Hugli 1999; Takabayashi et al. 1996).

C. Chemokines

Chemokines represent crucial mediators of leukocyte recruitment to injured brain (Babcock et al. 2003; Eugenin and Berman 2003). Intracranial infiltration of blood-derived leukocytes is an important event contributing to neuroinflammation in the CNS. The recruitment of neutrophils across the BBB has been shown in animal models to be detrimental for intracerebral homeostasis, due to the release of proteases and free oxygen radicals, contributing to BBB damage and the development of cerebral oedema (Schoettle et al. 1990). Neurones and glial cells have the ability to produce chemokines in response to inflammatory stimuli. The chemokine IL-8 has been reported to be increased in intrathecal samples following TBI and in much higher quantities than concurrent serum samples (Kossmann et al. 1997). It has been suggested that IL-8 has a detrimental role following TBI, with a significant correlation between intrathecal IL-8 levels and posttraumatic BBB dysfunction and mortality (Kossmann et al. 1997; Whalen et al. 2000). In contrast to the potential detrimental effects of IL-8 in injured brain, recent data has suggested trophic and regenerative effects, particularly in the CNS. In vitro studies have
demonstrated astrocyte and microglia proliferation in culture and the induction of nerve
growth factor in cultured astrocytes, while in vivo studies have shown de novo
angiogenesis in mammalian tissue in the presence of IL-8 (Araujo and Cotman 1993;

**Neurotransmitters and Injury-Induced Metabolic Cascade**

A. *Excitatory amino acids*

Excitatory amino acids (EAAs) normally function as neurotransmitters but are known to
be neurotoxic in high concentrations (Baker et al. 1993; Matute, Domercq, and Sánchez-
Gómez 2006). Glutamate is the principal excitatory neurotransmitter in the CNS.
Following glutamate release, post-synaptic responses occur via metabotropic and
ionotropic receptors. Metabotropic receptors mediate their action through GTP-binding-
protein-dependant mechanisms mobilising calcium (Ca\(^{2+}\)) from internal stores. Activation
of ionotropic receptors leads to permeability to sodium (Na\(^{+}\)), potassium (K\(^{+}\)) and/or Ca\(^{2+}\)
in associated ion channels (Arundine and Tymianski 2004). Microdialysis studies have
shown that increased concentration of brain interstitial EAAs exist in animal models of
TBI and that concentration of extracellular EAAs are related to the severity of TBI (Faden
et al. 1989; Rose et al. 2002). Furthermore, the use of inhibitors of EAA receptors in
animal models of TBI have demonstrated improved behavioural outcomes. In humans
high levels of EAAs have been found in the CSF following TBI, which can last for up to
several days (Baker et al. 1993; Zhang et al. 2001). It is believed that excess glutamate
acts as an agonist at gated ion-channels, leading to cellular oedema and accumulation of
intracellular Ca\(^{2+}\) and Na\(^{+}\), with subsequent lethal and sub lethal excitotoxic effects (H
Zhang et al. 2001).
B. Reactive Oxygen Species (ROS)

The role of ROS in the early phase of post-traumatic brain injury has been demonstrated in experimental studies. In one study an increase of more than 300% in the formation of hydrogen peroxide (H$_2$O$_2$) in rat brain extracellular fluid was demonstrated a few minutes after penetrating trauma (Layton, Pazdernik, and Samson 1997). The activity of two antioxidant enzymes that detoxify H$_2$O$_2$ (glutathione peroxidase and catalase) was also seen to significantly increase in rats following brain trauma. Following TBI there is an increase in intracellular calcium, which can result in the release of ROS from mitochondria (Stelmasiak, Dudkowska-Konopa, and Rejda 2000). Calcium overload also activates nitric oxide synthase and xanthine oxidase, which leads to increased ROS and nitric oxide (NO) production. ROS radicals in the presence of NO form peroxynitrates, which are known to damage the cytoskeleton and cell membranes (J S Beckman et al. 1990). An excess production of ROS may induce lipid peroxidation, which plays a crucial role in posttraumatic neural degeneration. In a recent human study, measurements of a lipid peroxidation by-product and an enzymatic anti-oxidant defence mechanism, demonstrated a significant increase in their levels reaching a peak within the first 20-24 hours after trauma (Paolin et al. 2002). This suggests a significant ROS-mediated oxidative stress associated with brain trauma and confirms the timing seen in experimental injury (Shohami et al. 1999). This human study also demonstrated that higher oxidative markers were associated with poor neurological outcome.

To date, studies in the use of free radical scavenger compounds in severely head injured patients have not shown any significant improvement in neurological outcome (Marshall et al. 1998; Young et al. 1996). Potential explanations include: patient heterogeneity, difficulty defining the time window for administration and the dosage regime and limited access to free radical production sites (Maas et al. 1999).
Cerebral ischaemia

Cerebral ischaemia refers to the inadequate delivery of oxygen to the brain. In one series of 112 neuropathological examinations in patients who died following TBI, 88% demonstrated evidence of ischaemic damage (D I Graham et al. 1989). Cerebral ischaemia is considered to be the single most important cause of secondary brain damage following TBI (Sahuquillo et al. 1993). Ischaemia often results from the disruption of normal cerebral autoregulation, with uncoupling of cerebral blood flow (CBF) and metabolism. In the early stages of TBI (within 10 hours), CBF often decreases (Overgaard and Tweed 1974). Later in the clinical course (24-72 hours) a low-flow state may persist or hyperaemia may occur (Zubkov et al. 2000). Hyperaemia is a result of an increased CBF beyond metabolic requirements and results in cerebral oedema and a rise in intracranial pressure (ICP). Cerebral perfusion pressure (CPP), which is calculated by subtracting ICP from mean arterial pressure (MAP) and is an indication of the pressure driving blood flow across the brain, therefore becomes impaired. Hyperaemia may be seen at any time in the first week after injury and has been reported in up to 30% of patients with severe TBI. It has been shown to have a marked deleterious effect on outcome (Zurynski, Dorsch, and Fearnside 1995; Muttaqin et al. 1993a). In one report, up to 30% of patients with a fatal non-missile head injury had moderate to severe ischaemic damage without raised intracranial pressure, which may reflect critical reductions in regional CBF (Graham et al. 1989). Cerebral ischaemia is not related only to disruption of cerebral autoregulation. Other causes of ischaemia include decreased arterial content, increased metabolic requirements or impaired tissue uptake.

The onset of post-traumatic cerebral artery vasospasm (PTV) can also result in ischaemia leading to secondary brain injury. Angiography is not routinely used in patients with severe TBI but transcranial doppler (TCD) has been used to measure blood flow velocity in the major cerebral arteries – most commonly the middle cerebral artery (MCA). Typically, TCD
velocity rises as vasospasm develops due to arterial narrowing, and has been demonstrated by comparing the results of cerebral angiography with TCD velocities (Lindegaard et al. 1989). However, TCD velocities can also rise as a result of increased volume flow. Studies have used the ratio between intracranial flow velocity and velocity in the extracranial (cervical) portion of the internal carotid artery to differentiate between PTV and hyperaemia (Muttaqin et al. 1993b; Zurynski, Dorsch, and Fearnside 1995). In both trauma and subarachnoid haemorrhage (SAH) patients, a ratio of greater than three was assumed to represent spasm, as a result of increased flow velocity in the MCA and reduced flow in the internal carotid artery due to increased cerebrovascular resistance (Weber, Grolimund, and Seiler 1990; Lindegaard et al. 1989). Studies of this nature are difficult to perform. Inter-observer variability exists in the evaluation of angiographic images and TCD is dependent on a co-operative patient, a patent temporal window and experienced operators. This is evidenced by the wide-ranging incidences of PTV reported, depending on the detection methods (Macpherson and Graham 1978; Oertel et al. 2005; Suwanwela and Suwanwela 1972; M Weber, Grolimund, and Seiler 1990). One study demonstrated that using TCD, 40% of their severely head injured population met the criteria for PTV (Zurynski, Dorsch, and Fearnside 1995). The development of PTV correlates with the presence of severe traumatic SAH on the initial CT scan, and the location of spasm with the location of haemorrhage (Zubkov et al. 2000; Zurynski, Dorsch, and Fearnside 1995). There is also an increased risk of developing PTV with an extradural haematoma, subdural haematoma or intracerebral haematoma on the initial CTB. PTV has been shown to develop most commonly on day two to three post-injury and generally last for a shorter period of time than aneurysmal vasospasm (Oertel et al. 2005; Zubkov et al. 2000). The presence of PTV has been associated with worsened outcome after traumatic brain injury (Zurynski, Dorsch, and Fearnside 1995).
In the management of severe traumatic brain injury the prevention, detection and management of identifiable ischaemia risk factors is one of the mainstays of treatment (www.braintrauma.org).

The pathways of secondary brain injury are important in understanding the complex cascades that are set in motion following TBI. Although they have the potential to be modified experimental therapies have not translated to the bedside. As a result, the clinical burden of secondary brain injury persists. As clinicians have little in their inventory to directly battle secondary brain injury one of the main aims of TBI management is to prevent potential secondary exacerbations by avoiding secondary insults.

1.1.5 Secondary Insults

Prevention of secondary insults is key in the management of severe TBI and clinicians monitor closely for such events including; hypoxia, hypotension, hyperglycaemia and raised temperature. Secondary insults can occur in both the pre-hospital and hospital settings and the injured brain appears to be highly sensitive to these insults when compared to the non-injured brain in experimental studies (Dietrich et al. 1996). In animal studies there is also some evidence to suggest that the brain is more vulnerable to secondary insults in the early stages following injury (Geeraerts et al. 2008). Secondary insults are thought to augment the secondary injury pathways set in motion following TBI and a growing body of evidence suggests that secondary insults not only occur frequently but may also have an influence on outcome post-TBI (Fritz and Bauer 2004; Natale et al. 2000; Kilpatrick et al. 2000).

Hypotension

Hypotension after trauma is a well-known independent predictor of death and multiple organ failure (Chesnut 1997; Shafi and Gentilello 2005b; Chesnut, Marshall, et al. 1993). Studies
concentrating on the early resuscitation phase following TBI, not only confirm that hypotension is common but is associated with a significant increase in mortality and morbidity (Chesnut, Marshall, et al. 1993; Chesnut, Marshall, et al. 1993; Jeffreys and Jones 1981; Manley et al. 2001). The impact of hypotension following TBI is not restricted to the early resuscitation phase (Chesnut 1997). Hypotension in the first 24 hours from injury was shown to increase mortality in patients with TBI, from 45% to 83%, when compared to similar patients without hypotension (Newfield 1980). In the ICU setting, patients were also at risk from hypotension. In one series one or more episodes of hypotension was recorded in 73% of TBI patients, using a computerised data collection system. They also found that hypotensive insults were associated with an increased mortality 12 months post injury (Jones et al. 1994). Many studies have suggested that the mortality associated with hypotension in those who have sustained a TBI is worse than in trauma patients without brain injury however, one group demonstrated that although hypotension was an independent risk factor for mortality it did not increase mortality in TBI more than in non-TBI patients (Shafi and Gentilello 2005a). In animal studies, haemorrhagic hypotension in the presence of TBI has been shown to reduce cerebral perfusion pressure and reduce the amount of oxygen carriers contributing to the already reduced brain tissue oxygenation (Matsushita et al. 2001). Hypotension also aggravated TBI-induced structural damage as reflected by a significant increase in contusion volume (Kroppenstedt et al. 1999). Clinical guidelines from the Brain Trauma Foundation (BTF) recommend that hypotension (Systolic blood pressure <90mmHg) should be avoided in both the pre-hospital and hospital settings (Badjatia et al. 2008; Anon. 2007).

**Hypoxia**

Pre-hospital hypoxia occurs frequently following TBI and has been associated with increased morbidity and mortality (Chi et al. 2006). One group found 57% of patients with a TBI had
inadequate oxygen saturations at the trauma scene prior to endotracheal intubation (Stocchetti, Furlan, and Volta 1996). In a retrospective review of the first 48 hours following injury 45% of patients experienced at least one episode of hypoxia (Jeremitsky et al. 2003). In the ICU setting the duration of hypoxaemia was found to be a significant predictor of mortality (Jones et al. 1994). The combination of hypoxia and hypotension dramatically affects mortality (Chesnut 1997).

BTF guidelines recommend that oxygen saturation <90% in the field and PaO₂ <60mmHg in the hospital setting, should be avoided (Bajdajia et al. 2008; Anon. 2007).

**Hyperglycaemia**

Hyperglycaemia has been shown to worsen long-term outcome after out-of-hospital cardiac arrest, myocardial infarction, stroke and critical illness (Longstreth and Inui 1984; Malmberg 1997; Pulsinelli et al. 1983). Retrospective reviews have demonstrated that hyperglycaemia is common following TBI and is associated with worsened neurological outcome (Jeremitsky et al. 2005; Lam et al. 1991). In a study of TBI patients a significantly worse outcome with glucose levels >200mg\(\text{dL}^{-1}\) (11mmol\(\text{l}^{-1}\)) was demonstrated (Lam et al. 1991). The underlying mechanisms by which hyperglycaemia may exacerbate secondary brain injury are unclear. Potential mechanisms have been suggested by animal models and include increases in EAAs, alterations in neuronal pH, lactic acid production and hyperosmolarity (Jeremitsky et al. 2005). Local policy suggests that blood sugar be maintained at 6-8mmol/l (Greater Manchester Neurotrauma Group - A framework for the management of traumatic brain injury; May 2003).

It is clear that TBI is devastating to both patients and their families. It continues to pose a challenge to treating clinicians who aim to provide the best care and achieve the best possible outcome. However, the heterogeneous nature of TBI coupled with the complicated and
connected pathways of secondary brain injury make it a difficult condition to manage.

Currently one of the goals of TBI management is to prevent secondary insults which could further exacerbate secondary injury. A raised temperature following TBI is considered by many to be a potential secondary insult and will be discussed further.
1.2 Temperature Following Traumatic Brain Injury

1.2.1 Temperature

It is unclear when monitoring temperature became part of routine practice, but current conventions are based on observations carried out more than a century ago. It was the work of Wunderlich in 1868 that led to the concept of ‘normal’ body temperature. He introduced a mercury axillary thermometer in 1851, which has recently been shown to be calibrated by 1.4 to 2.2 °C higher than instruments used today (Mackowiak 1998). From his observations, Wunderlich derived normal body temperature to be 37°C (range 36.2 to 37.5°C). He also developed one of the first quantitative definitions of ‘fever’ as ≥38°C (Sund-Levander, Forsberg, and Wahren 2002).

In a population of healthy volunteers between 18 and 40 years, a study examining oral temperatures measured over three days, demonstrated a range of temperature from 35.6°C to 38.2°C. This study also demonstrated a diurnal variation with a maximum oral temperature of 37.2°C at 06:00 and 37.7°C at 16:00. The author suggests that the use of 37°C as normal body temperature should be abandoned (Mackowiak, Wasserman, and Levine 1992). In a systematic literature review the range of normal temperature, depending on site of measurement, was much greater than that determined in the 1900’s. This review also suggests that the range of ‘normal’ temperature used today should be adjusted and that age and gender need to be taken into account (Sund-Levander, Forsberg, and Wahren 2002).

Human studies involving temperature measurements use a wide range of thresholds for what is ‘normal’ and what is elevated. In this thesis the common conventional standards of normothermia (37°C) and raised temperature (38°C) are used, in contrast to the temperature thresholds used by Stocchetti et al. in a study of the impact raised temperature on neurochemistry and brain oxygenation. They suggest that, as the Society for Critical Care
Medicine defines a ‘fever’ as an oral, rectal or central temperature of $\geq 38.3^\circ C$ and as brain temperature ($T_{\text{brain}}$) has been shown to be $0.4^\circ C$ higher than core temperature at the febrile peak; a raised $T_{\text{brain}}$ should be $\geq 38.7^\circ C$. They arbitrarily define normal $T_{\text{brain}}$ as $38^\circ C$, which this thesis uses as the threshold for elevated temperature (O'Grady et al. 1998; O'Grady et al. 2008; Stocchetti et al. 2005). Despite temperature measurement being a routine observation in all facets of daily clinical practice, our standards for ‘normal’ temperature and ‘fever’ are based on figures from the 19th century and may need to be re-assessed.

1.2.2 Raised Temperature

A raised temperature following TBI is commonly and interchangeably described as pyrexia, fever or hyperthermia. While pyrexia simply describes an abnormally elevated temperature, both fever and hyperthermia have clear definitions and their interchangeable use is erroneous. Fever has been described as a state of elevated core temperature, which is often but not necessarily, part of the host’s defensive responses to invasion of micro-organisms or inanimate matter recognised as pathogenic or alien by the host’ (Mackowiak 1998). Hyperthermia differs from fever as pyrogenic cytokines are not directly involved and standard anti-pyretics are ineffective. It represents a failure of thermoregulatory homeostasis, in which there is uncontrolled heat production, inadequate heat dissipation or defective hypothalamic thermoregulation.

The nature of raised temperature, particularly in the acute phase following TBI, has not been established.

1.2.3 Frequency of Raised Temperature following Traumatic Brain Injury

A raised temperature is common in neurosurgical ICU following TBI (Albrecht, Wass, and Lanier 1998; Jones et al. 1994; Kilpatrick et al. 2000; Rossi et al. 2001; Stocchetti et al.
One study reported that over 50% of patients with a severe closed head injury had a rectal temperature ($T_{\text{rectal}}$) greater than 38.5°C during their ICU admission, and that a single episode of raised temperature was a risk factor for subsequent episodes of raised temperature (Kilpatrick et al. 2000). Another group reported that 73% of patients admitted to ICU with severe TBI developed a raised temperature (greater than 38.4°C internally or 38°C externally) within the first week of injury (Stocchetti et al. 2002). In these retrospective studies temperature measurements varied from hourly to six hourly. Several risk factors for an early raised temperature following TBI on ICU were identified by another group. In particular a white blood cell count $>14.5\times10^9\text{l}^{-1}$ and a tympanic temperature of $>36^\circ\text{C}$ on admission were strongly associated with at least one episode of ‘hyperthermia’ within two days (Geffroy et al. 2004).

### 1.2.4 Temperature Measurement

The human body can be considered as two thermal compartments: a core compartment consisting of the viscera and a shell consisting of skin and subcutaneous tissue. Core body temperature is normally tightly regulated. The peripheral compartment is less strictly controlled and is usually 2-4°C below the core temperature. Limiting or increasing peripheral heat loss through vasoconstriction or vasodilation regulates core temperature. Physiological heat loss is achieved through changes in skin perfusion (vasoconstriction or vasodilation of blood vessels) and vaporisational heat loss via sweat production. There is evidence to suggest that brain temperature ($T_{\text{brain}}$) is dependent on three major factors: a) the production of local heat by metabolic processes; b) the rate of local cerebral blood flow; and c) the temperature of incoming arterial blood (Rumana et al. 1998a). In many ICU units it is not possible to measure $T_{\text{brain}}$ directly and as a result substitutes for $T_{\text{brain}}$ are often used.
**Peripheral Temperature Measurement**

It is well known that peripheral temperature is influenced by ambient temperature and also by local changes in the superficial vasculature. One study showed that in normal individuals exposed to mild hypothermia there was a wide temperature variation (up to 7ºC) between torso skin measurements. They also found that skin temperature was influenced by body shape and size and fatty deposits (Frim et al. 1990). Another group found that the difference in skin temperature was particularly significant along the vertical axis of the body, with differences of up to 9ºC (Zhu and Xin 1999). The numerous local influencing factors make peripheral temperature measurements a poor substitute for core or brain.

**Core Temperature**

Sites that are routinely used for core temperature measurement include rectum, bladder, oesophagus, nasopharynx, and tympanum. Each method for measuring core temperature has its own associated problems (Appendix B). From the available literature, it would appear that core temperature is not always a true representation of $T_{\text{brain}}$. Tympanic temperature measurements have been shown to be influenced by, the presence of cerumen, alterations in blood flow and user variability (Doezema, Lunt, and Tandberg 1995; Moran et al. 2007; Amoateng-Adjepong, Del Mundo, and Manthous 1999). When compared to pulmonary artery temperature in critically ill patients, tympanic temperature was found to be a poor substitute (Moran et al. 2007; Nierman 1991). Another group examined standard temperature monitoring sites compared with $T_{\text{brain}}$ during intra-operative induction and reversal of profound hypothermia. They demonstrated that during episodes of temperature flux, tympanic readings did not consistently reflect $T_{\text{brain}}$ (Stone et al. 1995).

In patients with TBI, it has been shown that $T_{\text{rectal}}$ is not a predictable substitute for $T_{\text{brain}}$ and that brain-rectal temperature differences ranged from 1.8 to -2.9ºC (Childs et al. 2005).
These authors also found that on average $T_{\text{brain}}$ did not exceed systemic temperature, which contradicts the findings in an earlier study which suggested $T_{\text{brain}}$ was on average 1°C higher than $T_{\text{rectal}}$ (Rumana et al. 1998a). Both groups did however show that there was considerable variation in individual brain-rectal temperature gradients which could not be predicted based on clinical findings. Similar findings have also been observed in patients with TBI at extremes of temperature, suggesting that $T_{\text{rectal}}$ under represents $T_{\text{brain}}$ (Henker, Brown, and Marion 1998). Bladder temperature is influenced by urinary flow and has also been shown to inadequately represent $T_{\text{brain}}$ following TBI and intra-operatively (Henker, Brown, and Marion 1998; Stone et al. 1995). Nasopharyngeal temperature is easily measured but has been shown to be dependent on the position of the probe and can deviate from $T_{\text{brain}}$ particularly at times of temperature flux (Stone et al. 1995).

**Brain Temperature**

Direct measurement of $T_{\text{brain}}$ is, considered by many, the gold standard in the management of patients with severe TBI on neurosurgical ICU. It is often not measured directly due to concerns of potential damage that could result from temperature probe insertion (Bommadevara and Zhu 2002). Human and animal studies have shown that a temperature gradient exists in the mammalian brain, with the core of the brain being warmer than the surface. The difference between core temperature and epidural space is usually 0.5°C but can reach 1.0°C (Mellergård 1994; Mellergård 1995; Zhu et al. 2006). Currently, a single intraparenchymal temperature measurement is generally assumed to be a reasonable reflection of brain temperature but the temperature variations across the brain following injury is unknown (Childs 2008). However, in a cohort of patients with intracranial pathologies admitted to ICU, no statistically significant difference in intraventricular temperature and different depths of intraparenchymal temperature was reported (Fountas et al. 2004). Currently, when $T_{\text{brain}}$ measurement is performed, it is measured at different
intracranial sites (intraventricular, intra-parenchymal or subdural) with a number of different sensor brands (Childs, Vail, Protheroe, King, & Dark 2005). There is no consensus among clinicians and researchers about temperature probe brand or site of placement, as intraventricular, intra-parenchymal and subdural temperature probes are all currently available. No evidence is available as to whether areas of injured brain, such as contusion, should be avoided when inserting the probe.

1.2.5 Raised Temperature Following Traumatic Brain Injury

The association between elevated temperature and outcome following TBI remains a source of ongoing debate. Results from animal models of TBI have been inconsistent. In rat models, delayed hyperthermia (39ºC for 3 hours) resulted in an increased mortality when compared to those maintained at normothermia (Dietrich, Alonso, Halley, & Busto 1996). These rat models also demonstrated that delayed hyperthermia aggravated histopathological damage with increased contusional volume, higher frequency of ischaemic neurones, moderate to severe BBB breakdown and an increased number of abnormally swollen axons. On the other hand, another group demonstrated no difference in behavioural outcomes in rats that had their temperature raised to 40ºC for one hour when compared to rats maintained at normothermia, in the immediate post-traumatic period (Clifton et al. 1991). In animal models of ischaemia, both early and delayed rises in temperature have resulted in increased mortality, severity of histopathological damage and acceleration of ischaemic brain injury (Dietrich et al. 1991; Dietrich, Busto, Halley, et al. 1990; Kim et al. 1996).

Patient studies of TBI also show conflicting results. In one ICU study, patients with a raised temperature were more likely to have a prolonged ICU stay than those without a raised temperature. However, no relationship between the presence or duration of a raised temperature and 6-month GOS scores was identified (Stocchetti et al. 2002). A microdialysis
study of people with TBI and SAH, assessing the impact of temperature changes on
neurochemistry and cerebral oxygenation, demonstrated that during episodes of raised
temperature ($T_{\text{brain}} \geq 38.7^\circ C$), ICP rose slightly but insignificantly and that delivery of glucose
and oxygen to the brain changed in line with metabolic demand. The authors suggest that a
raised $T_{\text{brain}}$ may be well tolerated, as long as substrate and oxygen delivery remain adequate,
when cerebral ischaemia is not the main pathophysiological mechanism and when it does not
cause intracranial hypertension (Stocchetti et al. 2005). These findings were confirmed in a
later study of 72 patients with severe TBI. No reduction in brain oxygenation during
episodes of raised temperature ($T_{\text{brain}} \geq 38.1^\circ C$) was reported; in fact episodes of brain hypoxia
were more frequent during times of normothermia (Spiotta et al. 2008). In a large study of
patients with brain injury (including TBI), in which data was collected prospectively and
analysed retrospectively, the impact of a raised temperature was augmented with the degree
of temperature rise. ICU length of stay was increased by 1.5 days in those patients with a
small rise in temperature (37.5-38.4$^\circ C$) but by 7.7 days in those with a high rise in
temperature (>39$^\circ C$). Similarly, small rises in temperature had no impact on mortality rate
while in those with the highest temperatures the mortality rate was tripled (Diringer et al.
2004). Of note, >90% of temperatures were measured orally, a method considered to be a
poor substitute for $T_{\text{brain}}$. A number of other studies have suggested that a post-traumatic rise
in core temperature is not only associated with an increased length of stay on ICU but, is also
an independent predictor for worsened outcome in both children and adults (Diringer et al.
2004; Natale et al. 2000; Suz et al. 2006). These studies were carried out for various lengths
of time post injury and used varying sites of temperature measurement including oral,
tympanic and rectal. It is also difficult to clarify whether increased mortality reflected
underlying infective processes or raised temperature itself.
Seminal publications in human stroke studies have demonstrated that admission temperature is highly associated with stroke severity, mortality and outcome and a raised temperature was associated with poor outcome (Reith et al. 1996; Azzimondi et al. 1995). In both of these studies temperatures were measured using sites thought to poorly represent core temperature. The evidence that fever following stroke is associated with a worsened outcome has been widely embraced and it is often assumed that this evidence can be translated to patients with severe TBI. However, as the initial mechanisms of injury, injury progression and patient population are different; it is difficult to justify this assumption.
1.3 Temperature Management Following Traumatic Brain Injury

Management of temperature following TBI remains controversial. Some of those involved in the care of patients following severe TBI advocate the induction of hypothermia while others aim to avoid a raised temperature and therefore maintain temperature at normothermic levels.

1.3.1 Induced Hypothermia

Induced hypothermia has been advocated as a neuroprotectant since the early 1900’s. Interest in its use following TBI has been re-ignited, particularly in light of improved outcome with its use following out-of-hospital cardiac arrest (Bernard et al. 2003; Yanagawa et al. 1998; Hinchey et al. 2010). The prevailing view that high temperature is harmful in patients following TBI has led to a number of animal and human clinical trials of cooling in TBI. Animal models of TBI have not given definitive or consistent results in the field of induced hypothermia. Following severe TBI, some rat models have shown not only reduced mortality and improved behavioural outcome but also reduced histopathological damage when treated with induced hypothermia compared to those maintained at normothermia (Clifton et al. 1991; Dietrich et al. 1994) In these experiments the authors also found that hypothermia significantly reduced the sum of necrotic neurones and contusional volume in the injured rat brain (Dietrich et al. 1994). Other studies have demonstrated a reduction in blood brain barrier disruption, attenuation of the release of EEAs and reduction in hydroxyl radicals (Globus et al. 1995; Jiang et al. 1992). However, the benefits of induced hypothermia have not been replicated in other animal studies. One study evaluated the effect of induced hypothermia on severe TBI with a secondary insult (moderate hypoxaemia and associated mild hypotension). The investigators found no difference in motor performance, cognitive performance, lesion volume or hippocampal neuronal survival with the application of
hypothermia for four hours following severe TBI with secondary insult compared with those managed at normothermia (Robertson et al. 2000). Another group examined chronic changes in rat brain following TBI. They did not reproduce any necrotic volume differences in rats managed with a period of immediate hypothermia or normothermia, although they did demonstrate significant decrease in the degree of ventricular expansion in those managed with hypothermia (Bramlett et al. 1997). No reduction in brain lesion volume was identified five days following TBI in immature rats managed with hypothermia compared to normothermia (Mansfield et al. 1996). Animal studies in the field of ischaemia consistently demonstrated significant protection to vulnerable brain areas using induced hypothermia (Busto et al. 1987; Dietrich, Busto, Valdes, et al. 1990; Dietrich, Busto, Halley, et al. 1990).

In patient studies, the initial seminal randomised trials of hypothermia in TBI were promising (Clifton et al. 1993; Marion et al. 1993). These single-centre studies suggested that moderate hypothermia (32-33ºC) had positive effects on cerebral metabolism and improved neurological outcome. Although the target temperature was similar for both trials, there were differences in protocol, for example the study of Marion et al. cooled for 24 hours only, while Clifton et al cooled for 48 hours. Neither achieved target temperature rapidly (within 7-10 hours of injury). Marion et al. measured T_{brain} directly while Clifton et al. measured core temperature for those randomised to hypothermia and either bladder or rectal for those randomised to normothermia. A large prospective multi-centre randomised trial followed but did not yield the clinically significant improved outcomes expected (Clifton et al. 2001). Moderate hypothermia (32.5-34ºC) did not improve outcome compared with normothermia. Following the publication of this study, many neurotrauma centres worldwide discontinued the induction of hypothermia following severe TBI. There are however some controversial issues in the interpretation of the data from this study. Firstly, the use of bladder temperature in TBI patients may not have accurately reflected T_{brain} at a given time. Secondly, the
observed slow (mean of 8.4+/−3.0 hours) induction of hypothermia may have been crucially affected the results, as very early induction is considered by many to be the key to neuroprotection. The use of small participating centres with little experience of induced hypothermia could also be criticised. There appeared to be varied results from the participating hospitals, with outcomes after hypothermia appearing more favourable in larger centres with more experience of dealing with induced hypothermia and its potential complications (Clifton et al. 2001). It is possible that the participation of small, inexperienced centres may have diminished the quality of the obtained data, and the poorly managed complications of hypothermia may have negated any potential benefits.

Further studies have since been published that suggest improved clinical outcome using induced hypothermia following TBI (Polderman et al. 2002; Qiu et al. 2007; Zhi, Zhang, and Lin 2003). In a study of hypothermia as an option of last resort in cases of ICP refractory to all other treatments, improved outcome was noted, particularly in patients with a GCS of 5 or 6 at the time of admission (Polderman et al. 2002). In this study great emphasis was placed on appropriate precautions and countermeasures for hypothermia induced complications.

One of the largest studies published in this field also demonstrated improved outcome with the use of induced hypothermia (Zhi, Zhang, and Lin 2003). Both of these studies maintained hypothermia for longer and re-warmed more slowly when compared with the earlier studies. In 2007, one study examined the effect of mild hypothermia in patients following a unilateral decompressive craniectomy for TBI. This group found that, when compared to a normothermia control group, there was improved neurological outcome despite an increased incidence of pulmonary infection in the treated group.

Recently a clinical trial, focusing on younger adults (16–45 years) with TBI, aimed to induce hypothermia (33°C) within 4 hours of injury. The trial was stopped following futility analysis as there was no improvement with hypothermia treatment (Dietrich and Bramlett
2010). The North America Brain Injury Study: Hypothermia results are awaited. Enrolled patients are assigned to a control normothermia group or a hypothermia group. The aim in the hypothermia group is to achieve a temperature of <35°C within 2.5 hours from injury and 33°C by 4 hours. Outcome will be assessed at 6 and 12 months. A recent review of the evidence for the use of induced hypothermia as a neuroprotectant following TBI, acknowledges promising results from single site studies in limited patient populations but also comments on the failure to translate these promising results to larger multi-centre trials. The authors suggest that continued investigations, including well designed and controlled clinical trials, are necessary. A Cochrane review of current evidence has not supported the routine use of induced hypothermia in TBI patients and suggested its use should be limited to good quality randomised controlled trials (Sydenham, Roberts, and Alderson 2009).

In the field of stroke, practical difficulties in body temperature reduction in awake patients and small study populations have made it difficult to determine clear benefits of induced hypothermia. Large randomised clinical trials are still needed to examine the relationship between induced hypothermia and outcome following stroke (den Hertog et al. 2007). Currently, there is no conclusive evidence that induced hypothermia is of benefit in TBI patients.

1.3.2 Maintained Normothermia

Because there is no clear evidence that induced hypothermia is beneficial and unease surrounding a raised temperature following TBI, many clinicians aim for the ‘middle ground’ in temperature management with a goal of maintenance of normothermia. This is despite no clear evidence that a raised temperature following TBI is harmful. There is little in the way of evidence surrounding maintained normothermia. One group maintained normothermia (T_{rectal} 36-36.5°C) in a small cohort of adult patients with a severe TBI using an intra vascular
cooling device and compared the results to a matched historical control group. This group was treated with conventional cooling treatments, in the form of anti-pyretics and surface cooling. Results demonstrated a decrease both in fever burden and ICP when compared to historical controls (Puccio et al. 2009). Problems with this study include the small patient numbers, historical nature of the control group and lack of information surrounding the conventional cooling treatments.

In our ICU at SRFT, clinicians aim to maintain normothermia where possible in TBI.

1.3.3 Management of Temperature Following Severe Traumatic Brain Injury in the UK and Ireland

In a survey of Neurosurgical ICU’s in the UK and Ireland, all units (33) measured temperature on a regular basis in patients with severe TBI (Appendix C). Skin folds (42%) were the most common site used for temperature measurement, followed by tympanic (27%), then other core temperature sites. The maintenance of normothermia was the temperature goal in most units (29) with only a small number of units (4) that automatically induced moderate hypothermia. A further nine units stated that they would consider the induction of hypothermia if a patient developed a raised ICP (Johnston et al. 2006).
1.4 Temperature Reduction

Methods of temperature reduction, whether to hypothermia or normothermia should ideally be swift to reduce $T_{brain}$ and with as few side effects as possible. In the UK and Ireland, a raised temperature following TBI most commonly results in the administration of paracetamol in an attempt to reduce the temperature. Surface cooling, in the form of air or water-cooling blankets or cold wet sheets, was the next most common method of temperature reduction (Johnston et al. 2006).

1.4.1 Pharmacological

Paracetamol is a derivative of p-aminophenol and demonstrates both analgesic and temperature reducing properties. It also has weak anti-inflammatory activity. Despite being available for more than 50 years the actual mechanism of action of paracetamol is still somewhat unclear. There has been debate recently regarding potential mechanisms of action. Some believe that its action is by selective inhibition of cyclooxygenase-3 (COX-3). Others believe that COX-3 is not independent but a splice variant of cyclooxygenase-1 (COX-1) and that paracetamol may act as a selective cyclooxygenase-2 (COX-2) inhibitor (Kis, Snipes, and Busija 2005; Graham and Scott 2005). Its anti-pyretic and analgesic effects are thought to be due to potent action on the CNS. It is believed to reduce temperature by lowering the hypothalamic set point, which is increased in true fever (Mayer et al. 2001).

Paracetamol is absorbed rapidly from the gastrointestinal system and peak plasma levels are reached in 30 minutes to one hour. Rectal administration leads to slightly slower absorption and peak plasma levels are reached after approximately one hour (Graham et al. 1990). The plasma half-life is 1.5 to three hours. It is generally a safe drug when used in recommended doses. In doses of approximately $140\text{mgkg}^{-1}$ or more, conjugation pathways become
saturated and alternative pathways convert paracetamol into a highly reactive intermediary metabolite. This can result in widespread hepatocellular damage.

Paracetamol is commonly used in the clinical setting to reduce a raised temperature. In one stroke study, paracetamol resulted in a small reduction in body temperature from baseline when compared to placebo in the first 24 hours following stroke. There was no significant effect on body temperature during the subsequent four days (Dippel et al. 2003). Another randomised trial in stroke patients also revealed only a small reduction in body temperature with the administration of paracetamol when compared to placebo (Kasner et al. 2002). Another group demonstrated that paracetamol had no effect on raised temperature (T_{rectal} >38.5°C) in critically ill patients (wide ranging pathologies including head trauma) in an intensive care setting (Poblete et al. 1997). In brain injured patients on ICU, the use of paracetamol was again shown to be poorly effective, with paracetamol failing to reduce temperature in 53.3% after 24 hours of treatment (Mayer et al. 2001). Despite evidence that paracetamol is not particularly effective in reducing a raised temperature, it continues to be the temperature reduction method of first choice in most neurosurgical ICU’s throughout the UK and Ireland (Johnston et al. 2006). Prior to the publication of this study, in one neurosurgical ICU the administration of paracetamol was nurse-led and the first-line agent used in all TBI patients whom developed a raised temperature.

Other pharmacological agents are available (e.g. Non-Steroidal Anti-Inflammatory Drugs), but they are not administered in the event of a raised temperature in our ICU and their use did not appear to be commonplace in other units throughout the country.

1.4.2 Surface Cooling

Unlike paracetamol, surface cooling does not alter the hypothalamic set-point in patients with raised temperature but does increase cutaneous heat loss. Numerous methods are used
in an attempt to promote heat loss by surface cooling. In febrile children tepid sponging is often used to promote heat loss. In one study sponging was found to be necessary for two hours and temperature often rose on cessation (Adam and Stankov 1994). In adults, surface cooling tends to be reserved for critically ill patients who are sedated, ventilated and paralysed, due to discomfort and potential reflex shivering. In a study of non-sedated stroke patients, surface cooling using an air-cooling blanket, achieved a modest temperature reduction without a worsening of outcome. Pethidine was required to prevent shivering and was administered on demand by the patient (Kammersgaard et al. 2000). In our ICU, surface cooling is achieved using wet sheets laid over the patient. Little evidence is available to support this method of surface cooling. One non-randomised crossover study of critically ill patients (including TBI patients) suggested that external cooling with cold wet sheets was effective at reducing temperature and also energy expenditure (Poblete et al. 1997). However, this study was not randomised and the sequence of treatments was chosen by the treating physician, which may have introduced bias.

Studies have been published examining the use of air/water-cooling blankets in brain-injured patients with a raised temperature. In one such study, Mayer et al. found no statistically significant difference between paracetamol alone and the addition of an air-cooling blanket in brain injured patients on ICU (Mayer et al. 2001). Several problems were noted with this study including, tympanic temperature measurement, significant numbers of protocol violations and nurse-led interventions in an already demanding clinical setting. In a small group of brain injured patients, no difference between paracetamol, tepid sponging and water-cooling blankets was found (Morgan 1990). In another study, the research group used a combination of two water-cooling blankets (above and below patient) along with water and alcohol sprays and exposure of areas not being directly cooled, to achieve the desired
hypothermic target (32°C) within 2 hours in 95% of patients (Polderman 2004; Polderman et al. 2002).

A novel surface cooling system (Arctic Sun, Medivance, Louisville, CO) which employs hydrogel-coated water-circulating energy transfer pads applied directly to the trunk and thighs, has been used in clinical trials. In a small group of brain injured patients on ICU, the use of this novel device resulted in a 75% reduction in fever burden (Mayer et al. 2004). This system also attained normothermia faster than a conventional water-cooling blanket. In another small study of brain injured patients the Arctic Sun device was also shown to rapidly reduce temperature (Carhuapoma et al. 2003). In a more recent small observational study this device was again shown to significantly reduce temperature in ventilated brain injured patients (Hata et al. 2008). Shivering was encountered frequently in these studies and there is a risk of skin ischaemia and necrosis, particularly in patients that often require vasopressors.

1.4.3 Gastric Lavage

Little information is available regarding the effectiveness of temperature reduction using gastric lavage, although it has been mentioned as part of conventional methods of temperature reduction (Diringer 2004; Marion et al. 1993). In our neurosurgical ICU, gastric lavage has been used in TBI patients with a raised temperature resistant to other reduction methods. Anecdotally, the ICU medical and nursing staff, describe gastric lavage as a generally effective method of temperature reduction. The lavage is carried out by the nursing staff and has been found to be work-intensive. This can result in gastric lavage not being carried as regularly as outlined in the protocol and therefore reducing its efficacy. One other concern is the potential for large volumes of water to be absorbed from the duodenum leading to other problems such as hyponatraemia. Although no literature is available regarding problems associated with gastric lavage in the cooling process, cases have been reported of
water intoxication following the ingestion of large volumes of water, particularly in patients suffering from psychiatric illness (Hayashi et al. 2005; Loas and Mercier-Guidez 2002; Chen and Huang 1995). One case is reported of iatrogenic water intoxication as a result of gastric lavage for ingestion of a presumed poison, which resulted in the death of the patient (Chen and Huang 1995). Problems with water intoxication range from mild to severe and can include hyponatraemia, cerebral oedema and visceral oedema.

1.4.4 Intra-vascular Cooling

Intra-vascular cooling has been achieved previously using ice-cold intravenous fluid. In a study of brain injured patients on ICU, temperatures were rapidly reduced to target (32-33°C) by the infusion of large volumes of refrigerated (4°C) fluids in conjunction with an ice-water-cooling blanket. They found that reduction of temperature was rapid and, with close regard for potential side effects, safe and effective (Polderman et al. 2005). Intravascular cooling devices are available. A typical device consists of three components: an external heat exchange and control unit, a heat exchange catheter and tubing set. The catheter simultaneously functions as a single or double lumen central venous catheter and can be placed in the subclavian or femoral veins. Normal saline is pumped from the control unit through the tubing set to two balloons coaxially mounted on the catheter in a closed loop that returns the saline to the control unit. The control unit alters the temperature of the circulating saline to maintain the patient’s temperature at the desired level. The addition of an intravascular cooling device to conventional methods of cooling, in a group of critically ill brain injured patients, was more than twice as effective at reducing fever burden as conventional methods alone in one study (Diringer 2004). This group found that it was also associated with less use of anti-pyretic agents, sedatives and narcotics and that its use was not associated with increased complications over and above that associated with the use of a
conventional central venous catheter. An earlier pilot study had published similar results and
also demonstrated that the intravascular cooling device was highly effective at reducing and
controlling body temperature in brain injured patients on ICU, with no additional morbidity
or mortality (Schmutzhard et al. 2002). The safety and efficacy of the intravascular cooling
device was further supported in a study of a small cohort of patients with severe TBI, in
whom normothermia was maintained (Puccio et al. 2009).

1.4.5 Selective Brain Cooling

In the UK the practice of selective brain cooling is not routine. One UK group undertook a
randomised control trial of the effects of airflow through the nasal passages on brain
temperature in brain-injured patients. They administered air at room temperature and
humidity via a sponge tipped oxygen catheter in each nostril. No clinically relevant or
statistically significant reductions in $T_{\text{brain}}$ were found (Andrews, Harris, and Murray 2005).
Another group performed a prospective randomised control trial to examine the effects of a
selective cerebral cooling system (‘Cooling cap’) in patients with severe TBI, when used for
24 hours followed by rewarming over 24 hours. When compared to a control group, which
were not treated with the ‘cooling cap’, they found no statistically significant difference in
$T_{\text{brain}}$ or outcome between the two groups (Harris et al. 2009).
1.5 Management of Traumatic Brain Injury

The control of ICP and CPP are considered cornerstones in the management of TBI on ICU.

1.5.1 Intracranial Pressure

The measurement of ICP is considered important following severe TBI as a tool for the early identification of evolving mass lesions in sedated patients. It is also required to calculate CPP. Many TBI management protocols are driven towards CPP targets however, there is a significant body of evidence that suggests ICP is an independent predictor of outcome following severe TBI (Balestreri et al. 2006; Helmy, Vizcaychipi, and Gupta 2007; Hiler et al. 2006; Miller et al. 1981; Narayan et al. 1982; Treggiari et al. 2007; Juul et al. 2000). The measurement of ICP is associated with its own controversies. These include the type of device which should be used for ICP measurement, placement of device and treatment thresholds. Current BTF guidelines suggest that with the technology available a ventricular catheter connected to an external strain gauge is the most accurate, low cost and reliable way of monitoring ICP. They also suggest that monitors placed within the subarachnoid, subdural or epidural space are less accurate than parenchymal or ventricular monitoring. A number of retrospective studies have shown that an ICP >20-25mmHg is a discriminatory factor between patients with potentially good and poor outcomes (Balestreri et al. 2006; Czosnyka et al. 2005; Hiler et al. 2006). As a result 20-25mmHg is regarded by many as a pathological threshold below which ICP should be maintained. BTF guidelines suggest that treatments should be initiated with ICP thresholds above 20mmHg. In the event of a rise in ICP treatments that may be initiated include, increased sedation, induction of hyperventilation, hyperosmolar therapy, barbiturate coma and consideration of surgical intervention. In relation to this study sedation and barbiturate coma will be reviewed.
Sedation

Different depths of anaesthesia can be achieved and, in our population of TBI patients, a state of unconsciousness is the desired clinical end-point. Unconsciousness is defined as a hypnotic state in which an individual is incapable of responding to sensory stimuli or having subjective experiences (March and Muir 2005). It also results in a reduction of cerebral metabolic rate of consumption of oxygen and facilitates mechanical ventilation (Helmy, Vizcaychipi, and Gupta 2007). In addition it prevents noxious stimuli leading to unwanted rises in ICP, which is particularly important for surface cooling. It is achieved using a combination of medications with both anaesthetic and analgesic qualities. Analgesia is dependent on the depression of ascending nociceptive signals prior to or after they reach the level of the dorsal horn of the spinal cord, brainstem reticular formation nuclei, thalamic nuclei and cerebral cortex (Antognini and Carstens 2002; Campagna, Miller, and Forman 2003; Prys-Roberts 1987). Inhibition of these pathways will prevent activation of the cerebral cortex and prevent corticocerebral perception of the noxious stimulus. Arousal from an apparent unconscious state may occur following a sufficiently noxious stimulus. The loss of purposeful motor response after a noxious stimulus is thought to be due to the inhibition of sensory pathways that activate motor centres or depression of descending motor pathways in the cerebral cortex, brainstem and spinal cord (Prys-Roberts 1987). Loss of reflex movement is usually due to inhibition of sensory or motor pathways at the spinal cord segmental level (Rampil and King 1996). External cooling processes can result in reflex shivering in order to generate heat and ‘fight’ the cooling process, due to an elevated hypothalamic set point.

In our institution, sedation is achieved with infusions of propofol and alfentanil. If additional sedation is required an infusion of midazolam may be added. Propofol is an intravenous anaesthetic agent, which is often used as a sedative in the critically ill. It has superior metabolic suppressive effects, when compared to midazolam, and a short half-life. It is not
recommended in hypothermic patients as it has a tendency to accumulate and precipitate hyperlipidaemia. Other problems associated with propofol include cardiovascular collapse and the propofol infusion syndrome of metabolic acidosis, rhabdomyolysis and bradycardia (Helmy, Vizcaychipi, and Gupta 2007). Alfentanil is an opioid drug that is thirty times more potent than morphine and is ideal for infusion. Midazolam is a water-soluble benzodiazepine with a short duration of action which is effective as both as a sedative and an anti-convulsant. In the case of a refractory ICP, a barbiturate coma may be induced and in our institution thiopentone is the barbiturate of choice. The effects of barbiturates are dose dependent and are known to cause reversible depression of cerebral function. They decrease cerebral blood flow and reduce cerebral metabolic usage of oxygen and glucose by fifty percent. As barbiturate load increases, neuronal activity decreases by increasing the conductance of GABA-regulating chloride channels which alters the wave and frequency of the electroencephalograph (EEG). The optimal state in barbiturate coma is to achieve burst suppression – periods of no EEG activity for 6 to 10 seconds and 3 to 5 bursts of EEG activity per minute. There are two main problems with the use of barbiturates. Firstly, they can cause significant episodes of hypotension and secondly, the prolonged half-life makes clinical assessment difficult once they have been stopped. Despite the ability of barbiturates to control ICP there is no clear evidence that its use improves outcome (Roberts 2000).

Sedation Scores

A wide variety of sedation scores are available to assist in the monitoring of depth of sedation. In our institution the sedation score is documented hourly. During the ongoing research programme on ICU, members of the research team noted that despite some TBI patients being assigned the lowest sedation score (unrousable), there was evidence (such as movement, biting on the endotracheal tube and cardiovascular changes) to suggest that the patient was not deeply sedated. This was particularly evident on the application of a noxious
stimulus. Many of the interventions carried out on ICU, including temperature reduction methods, have the potential to act as noxious stimuli. In those patients with a severe TBI who are inadequately sedated, a noxious stimulus may result in ICP and/or cardiovascular changes, therefore accurate knowledge of depth of sedation would seem to be of considerable importance. Anecdotally, there does not appear to be consistency between documented sedation scores and true depth of sedation in our ICU.

**Bispectral Index Monitoring (BIS)**

Bispectral analysis was first introduced in the 1960’s to study ocean wave motion, atmospheric pressure changes and seismic activity. It is a signal processing technique that is capable of tracking changes in signals arising from linear and non-linear changes in the generating process.

In recent years bispectral analysis has found a role in clinical practice with the development of bispectral EEG analysis. The Bispectral Index Monitoring System (BIS XP, Aspect Medical Systems, Newton, MA) was developed from a large database of EEG recordings and corresponding hypnotic states collected from normal healthy volunteers. A combination of clinical assessment, responsiveness to stimulation, plasma concentration of sedative/hypnotic agents and memory testing, determined hypnotic states. Multiple EEG features were correlated with clinical end-points following administration of sedative/hypnotic agents. Multi-variate statistical analysis was performed and the relevant EEG features combined to produce the BIS index – A value on a linear scale correlating with clinical endpoints of hypnotic state. In the absence of electromyography (EMG) interference a value of 100 corresponds with an awake state and a value at or near zero corresponds to minimal or absent brain activity. Additional clinical end-points and corresponding BIS values are found on a continuum between these extreme values.
BIS monitoring has been well established for use in the theatre setting. Its use in anaesthesia has been shown to reduce awareness, decrease the amount of anaesthetic agents used and facilitate recovery (Ekman, Brudin, and Sandin 2004; Gan et al. 1997; Myles et al. 2004; Song, Joshi, and White 1997).

BIS monitoring in the ICU setting is less well established and particularly in neuro-ICU. Several papers have examined the relationship of BIS with sedation scores on ICU patients. One group correlated BIS index with the Ramsay Sedation Score (RSS) in sedated patients with chronic obstructive pulmonary disease. They found that BIS index correlated with RSS and propofol dosage, and could potentially be useful in identifying possible dangerous clinical situations of over sedation (Mondello et al. 2002). In a heterogeneous group of ICU patients with no obvious brain injury, BIS correlated well with the Sedation-Agitation Scale (SAS), and was also found to be a good measure of hypnosis. This group also found that the correlation between BIS and SAS was better in trauma patients than for general or cardiac surgical or medical patients (Simmons et al. 1999). In a paediatric ICU population, BIS was also found to correlate with clinical sedation scores and to differentiate adequate from inadequate sedation (Berkenbosch, Fichter, and Tobias 2002). By contrast, another study could demonstrate a correlation between BIS and a number of sedation scales in only 58% of their population of ventilated surgical patients. In the 42% of patients in whom there was no correlation, no explanation for the discrepancy was found. The authors were unable to determine any discriminating factors that could identify patients suitable and unsuitable for BIS monitoring (Frenzel et al. 2002).

In patients with brain injury the evidence is more conflicting. In a population of patients with a non-traumatic brain injury requiring mechanical ventilation, BIS (XP version) strongly correlated with SAS, Richmond Agitation Sedation Scale (RASS) and GCS, regardless of the presence of sedative medications (Deogaonkar et al. 2004). Another group analysed the use
of BIS to predict recovery of consciousness in unconscious brain injured patients (including TBI) who had had their sedation switched off. They found that BIS values were significantly higher in patients who recovered consciousness compared to those who had a poor neurological outcome (persistent vegetative state or death). The maximum and mean BIS values had a high prediction probability, compared with traditional clinical measures, such as GCS (Fàbregas et al. 2004). BIS has also been shown to be potentially useful in the detection of brain death in brain-injured patients admitted to ICU with a GCS ≤5 (Vivien et al. 2002). A fall in BIS to zero in patients approaching brain death was demonstrated by this group. They also noted that interference between EEG and EMG was a potential problem, giving falsely high readings. Low-frequency EMG activity is known to potentially falsely elevate BIS values in anaesthetised patients without NMB and as a result NMB may be required if high EMG activity could interfere (Bruhn, Bouillon, and Shafer 2000). Other concerns have been raised about the reliability of BIS monitoring. Asymmetrical BIS scores in patients with abnormal CTB scans, large variances in BIS scores in patient with brain injury, electrocardiographic interference and metabolic disorders have all been reported as potential problems during BIS monitoring (Fodale and Pratico 2004). Interpreting the data regarding the usefulness of BIS in the ICU setting is difficult due to the heterogeneous populations studied, different methods of BIS data collection and use of different versions of BIS software and hardware. However, if the potential problems are considered BIS monitoring may be useful to the clinician by offering a continuous real-time assessment of the level of consciousness. It may also provide an early indicator of the progression of underlying disease.
1.5.2 Cerebral Perfusion Pressure

The maintenance of CPP is another cornerstone on the management of severe TBI. The aim of CPP maintenance is to ensure adequate perfusion of brain tissue and therefore sufficient substrate delivery. The first evidence that maintenance of CPP above a target threshold was beneficial was published in 1995. Although this study was non-randomised and used historical controls, it demonstrated an improved outcome if CPP was maintained >70mmHg (Rosner, Rosner, and Johnson 1995). Recent studies have suggested a CPP in the region of 50-70mmHg is appropriate following TBI, but aggressive maintenance of CPP >70mmHg should be avoided due to the risk of adult respiratory distress syndrome (Lin et al. 2008; Helmy, Vizcaychipi, and Gupta 2007; Anon. 2007). Aggressive maintenance of CPP may also result in passive increases in blood vessel diameter (due to loss of vascular autoregulation), increasing CBF and ultimately increasing ICP. In addition, increases in hydrostatic pressure across the cerebral capillary bed can lead to vasogenic oedema (Helmy, Vizcaychipi, and Gupta 2007). BTF guidelines recommend avoiding aggressive attempts to maintain CPP>70mmHg and avoidance of CPP<50mmHg. In the event of a reduction in CPP a vasopressors is often added, particularly if the intravascular volume is adequate. In our unit, noradrenaline is the vasopressors of first choice.

**Noradrenaline**

Noradrenaline is a naturally occurring catecholamine which acts as a neurotransmitter that is released from most sympathetic postganglionic fibres. It is a potent $\beta_1$ agonist and therefore increases myocardial inotropy. It is also a potent $\alpha$ agonist that results in vasoconstriction. This can have consequences particularly for surface cooling, as peripheral vasoconstriction may result in reduced peripheral heat loss. The use of some surface cooling methods may need to be used with caution or not at all, in a patient with peripheral vasoconstriction, as further compromise to skin blood flow could result in skin break down.
1.5.3 Avoidance of Secondary Brain Injury

The prevention of secondary brain exacerbation is key to the management of severe TBI. This would ideally be achieved by avoidance of secondary brain insults and maintenance of normal physiology. Identification of secondary brain injury is difficult in TBI; especially in ventilated patients. Although not used routinely in clinical practice in the UK and Ireland, S100b is a promising brain biomarker. It is postulated that serum measurement of S100b might not only assist in brain injury classification but also act as a marker of secondary brain injury.

S100b

S-100 is an acid protein with calcium-binding properties that was first described in 1965 (Moore 1965). S-100 is not a single component, but a mixture of similar proteins composed of two immunologically distinct subunits, the α- and β-subunits. To date 17 different proteins have been assigned to the S-100 family and it is believed that the S-100 proteins influence cellular response along the calcium-signal-transduction pathway, acting at different points along the cascade (Schäfer and Heizmann 1996).

The ββ form is known as S-100b and is found in high concentration in the nervous system of vertebrates. It has been found mainly in schwann cells and astrocytes but has also been detected in other tissues such as melanocytes, adipocytes, chondrocytes and epidermal langerhans cells (Hidaka et al. 1983; Stefansson et al. 1982; Stefansson, Wollmann, and Jerkovic 1982). Under normal circumstances S-100b is undetectable in serum, although using a technique sensitive enough to detect serum S100b in a group of healthy volunteers between 18 and 65 years of age, a median plasma level of 0.05 µg/l was found (Wiesmann et al. 1998). Following a brain injury S-100b is released as a result of glial cell damage and increased levels have been found in cerebrospinal fluid (CSF) following TBI, intracranial
tumours, hydrocephalus, encephalitis, meningitis, cerebral infarction and a variety of other neurological pathologies (Infante et al. 2003; Lamers et al. 2003). Normally detection of S-100b in serum occurs only if there has been alteration in the permeability of the blood-brain-barrier (BBB) and a rise in serum S-100b has been reported in TBI, ischaemic stroke and in patients with neurological complications following cardiac surgery (Anderson et al. 2001; Johnsson et al. 1995; Raabe, Grolms, and Seifert 1999).

There is some evidence to suggest that the use of serum S-100b may be useful to further classify patients with both mild and severe TBI. In mild TBI, S-100b has been suggested as a potential adjunct in the differentiation of the patients who will require follow-up due to disability (Townend et al. 2002). It is estimated approximately 15-50% of patients will develop sequelae, requiring follow-up; following mild head injury and S-100b may be of assistance in the presence of a normal CTB (Ingebrigtsen et al. 1995).

In severe TBI, S-100b levels > 2.0µg/l have been shown to be highly specific, although not sensitive, for predicting unfavourable outcome (Raabe et al. 1999). In this study of patients with severe TBI there were no survivors in patients with an S100-b level > 3.8µg/l, examined over a maximum ten day period following admission to ICU. In a more recent study of 100 patients with severe TBI, serum S100b levels measured 24 hours from injury were significantly higher in patients with an unfavourable outcome at three months (Rainey et al. 2009). In a population of TBI patients who became brain dead following severe TBI, median admission S100b levels were higher when compared to those who did not (2.32µg/l vs. 1.048µg/l) (Dimopoulou et al. 2003). A significant correlation has also been shown between S-100b and the contusion volume visible on CT scan (Raabe et al. 1998).

The release of S-100b following brain injury is believed to be instantaneous with rapid clearance thereafter (Ingebrigtsen and Romner 1996; Jackson et al. 2000). Early estimates of S-100b half-life were calculated to be approximately two hours. This estimate was based on

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65
analysis of S100-AO isoform in patients undergoing cardiac bypass. In the cardiac-bypass setting, the half-life of S-100b has recently been estimated at approximately 25 minutes (Jonsson et al. 2000). Serial measurements of serum S-100b in a small group of severely head injured patients, in a multi-trauma setting, suggests that the half-life is approximately three hours (Jackson et al. 2000). Ongoing release of S-100b with secondary brain injury has been demonstrated and this may account for the relatively prolonged half-life found in the severely injured (Rotheorl et al. 1999). The clearance characteristics of S100b following TBI have not been firmly established. This has a profound effect on the sample timing and on interpretation of results.

S-100b can be measured from arterial and venous blood. It does not require immediate centrifugation and freezing as it remains stable for a prolonged period of time and does not require specialised sampling or analysing techniques (Sapsed-Byrne, Gao, and Harris 1997).
1.6 Summary and Rationale for Research Studies

TBI poses a major clinical burden locally and nationally. Although the primary brain injury sustained at the time of trauma cannot be altered there is potential to modify secondary brain injury pathways. Currently there is little available to the clinician to directly alter secondary injury pathways following TBI and as a result the mainstay of management is to maintain normal physiology and avoid secondary insults that may augment secondary brain injury. There is no clear evidence that a raised temperature following TBI is truly harmful. However, many clinicians believe it has the potential to act as a secondary insult to an already vulnerable brain. As a result of this, in conjunction with a lack of evidence surrounding the benefits of induced hypothermia, most ICU’s in the UK and Ireland, including our own institution, aim to maintain temperature at ‘normal’ levels. Temperature reduction methods are primarily by way of paracetamol administration and surface cooling. In our institution gastric lavage is added if surface cooling has failed. These methods of temperature reduction are both time consuming and labour intensive. A preliminary audit carried out prior to the onset of this study suggested that, despite the efforts of the ICU staff, normothermia was rarely achieved. The audit also raised concerns regarding the depth of sedation of patients and physiological changes during episodes of surface cooling and gastric lavage. Temperature reduction methods in the form of surface cooling and gastric lavage are undertaken frequently and are presumed to be innocuous.

Studies Described in this Thesis

Patient Review

In order to assess outcome and temperature further in our own population of TBI patients, a retrospective review of all TBI patients admitted to SRFT ICU over a 12 month period was performed. The admission temperature and highest temperature at 48 hours and 120 hours
following injury were analysed along with outcome. At 48 hours and 120 hours following injury the length of time temperature was ≥38°C was also analysed with outcome. We aimed to determine whether there is any evidence that a raised temperature is associated with poor outcome in the population of patients with severe TBI admitted to our ICU.

**Observational Study**

An observational study was designed to study in detail the effect of cooling methods used in the step wise protocol in the event of a raised temperature following TBI. Patients were recruited for a maximum of 5 days and a maximum of two cooling episodes were studied during this period. The main aim of the observational study was to observe the effects of cooling on T_{brain} and whether T_{brain} was reduced to the ‘normothermic target’ temperature within the protocol time-frame. Cooling is often presumed to be innocuous but there is no evidence to support this assumption. The maintenance of ICP and CPP within target limits is considered vitally important in the management of TBI. As a result changes in these parameters were observed throughout the study period and in more detail during studied cooling episodes. The main aim of monitoring these parameters was to observe for any potentially detrimental changes in ICP and CPP that may be linked to the cooling processes. Closely linked with CPP and temperature reduction, noradrenaline requirements were also monitored during studied cooling episodes. Adequate sedation is important in patients following severe TBI and essential during cooling to prevent awareness of a noxious stimulus that could result in a rise in ICP and shivering. During studied cooling episodes BIS monitoring was carried out to monitor BIS trends and potential changes in conjunction with clinical interventions. Throughout the study period and more frequently during studied cooling episodes, blood samples were obtained for the brain biomarker S100b. Levels of this biomarker, particularly during studied cooling episodes, were examined for changes that could be consistent with secondary injury. Blood samples for the inflammatory cytokines IL-
6 and TNF-α were also sampled during the study period and more frequently during studied cooling episodes. The aim was to observe any changes in inflammatory response during studied cooling episodes.

In summary, the aim of this observational study was to observe the effects of the cooling methods employed in our institution on T\textsubscript{brain} and to monitor for changes in important physiological and biochemical parameters that may suggest cooling is not as innocuous as often presumed. It is hoped that this observational study will be the basis of future research on thermoregulation following severe TBI.
Chapter 2

Methods
This chapter describes the methods of two separate but linked studies in TBI patients admitted to SRFT ICU. The first study is a retrospective review of 57 patients, looking at the highest temperature each patient experienced and LoT temperature was $\geq 38^\circ\text{C}$ at different time points, in association with outcome. The second study is a detailed observational study of 8 patients, looking at cooling and changes in particular physiological and biochemical parameters.

2.1 Clinical

Setting

Both the observational study and patient review were undertaken in the Neurosurgical ICU of Salford Royal NHS Foundation Trust (SRFT). SRFT is an acute teaching hospital with 900 beds and 4500 staff. It is home to the Greater Manchester Neurosciences Centre (GMNC), which includes the Neurosurgical and ICU departments, along with Neurology and Stroke Services. The GMNC serves predominantly the population of Greater Manchester (Appendix D) but also the North West region of England as required.

Neurosurgical Services

The neurosurgical service is led by Mr. J Thorne (Clinical Director and Neurosurgical Consultant) along with 13 consultant colleagues. In addition to 77 ward beds there are 10 beds on a dedicated neurosurgical High Dependency Unit (HDU). There are very strong links with the intensive care, anaesthetic, neuroradiology, neurology and rehabilitation teams.

Intensive Care Services

The ICU is led by Dr. T. Thomas, with a team of 13 consultant colleagues. It is a 17-bedded general ICU, which at any one time can have a varying number of beds occupied by neurosurgical patients. Six of the intensive care team have a special interest in neurosurgical
intensive care. There are very close ties with the neurosurgical, neuroradiology and neurosurgical-HDU teams.

**Clinical Research Team**

This study and patient review forms part of an ongoing research programme on the neurosurgical ICU, studying human thermoregulation after brain trauma. The principal investigator was Dr. Charmaine Childs (Senior Research Fellow/ Honorary Senior Lecturer, University of Manchester). One clinical research fellow and a laboratory technician, along with support from the neurosurgical, intensive care and biochemistry staff, make up this research team. Since completion of this particular work, Dr Childs has moved to Singapore (Alice Lee Centre for Nursing Studies, Yong Loo Lin School of Medicine) to continue her research.

### 2.1.1 Clinical Protocols for TBI Management

All patients admitted to SRFT ICU following a severe TBI are managed according to local policy:

- Patients with a severe TBI requiring surgical intervention are immediately transferred to theatre. The patient is transferred to ICU following surgery. Patients not requiring immediate surgical input are transferred directly to ICU.
- All patients admitted to ICU following a severe TBI are intubated, ventilated and sedated. Intravenous propofol and alfentanyl are routinely used to achieve sedation, with the addition of a benzodiazepine (midazolam) if required. Neuromuscular blockade (NMB) is only added in specific circumstances such as refractory ICP.
- Full spine immobilisation is maintained until the cervical, thoracic and lumbar spine are radiologically examined and bony injury excluded.
- Patients are nursed with a head up tilt of 30°. The whole bed is tilted until the spine is cleared of injury.
• All patients have a central venous catheter (internal jugular, subclavian or femoral) and arterial line (radial, brachial or femoral) inserted in the local hospital or at the time of admission to SRFT ICU.

• Routine monitoring for patients with a severe TBI included measurement of:
  - ICP (single modality ICP monitoring or combined ICP/$T_{\text{brain}}$)
  - Electrocardiogram (ECG)
  - Pulse Oximetry
  - Arterial blood pressure (ABP)
  - MAP
  - CPP
  - Central venous pressure (CVP)
  - Heart rate
  - Body temperature
  - Rectal – Routinely measured in all patients with a severe TBI.
  - Tympanic – Measured if rectal or intraparenchymal temperature measurement was not available
  - Brain – Measured in a subgroup of patients that did not require immediate surgical intervention
  - Arterial blood gases
  - Blood sugar

Physiological parameters displayed on the bedside monitor are routinely recorded every 10 minutes via a bedside acquisition system (Marquette Electronics, Milwaukee, W1, USA).

• Therapies are aimed at maintaining CPP >60mmHg and ICP <20-25mmHg

• Noradrenaline is the vasopressor of first choice if CPP is not maintained at the desired level

• To maintain ICP<25mmHg standard methods are used – adequate sedation and analgesia, ensuring that there is no evidence of venous congestion, NMB and osmotherapy (mannitol). In the event of a rise in ICP refractory to standard treatments repeat imaging is performed. Boluses of barbiturate may be given at this stage.

• If repeat imaging reveals a lesion amenable to surgical intervention, the patient is transferred to theatre for emergency surgery. If no surgical intervention is warranted a barbiturate coma may be induced.

• In the event of a rise in $T_{\text{rectal}}$ or $T_{\text{brain}}$ $\geq 38^\circ$C for $>30$ minutes, a cooling protocol is initiated

• Enteral feeding is typically commenced a few hours following admission

• Antibiotics are only introduced if there is evidence of infection
2.1.2 Clinical Protocol for Temperature Management

Temperature measurement is performed in all patients admitted to ICU following a severe TBI. $T_{\text{rectal}}$ is routinely measured and continuously displayed on a bedside monitoring system (Marquette Electronics, Milwaukee, W1, USA). $T_{\text{brain}}$ is measured in addition to $T_{\text{rectal}}$ in a subgroup of patients not requiring immediate surgical intervention. This measurement is also continuously displayed. $T_{\text{rectal}}$ and $T_{\text{brain}}$ are electronically recorded every 10 minutes via the bedside monitoring system. In addition, the nursing staff document these measurements on an hourly basis. Tympanic temperature is measured if $T_{\text{brain}}$ and $T_{\text{rectal}}$ measurements are not available.

Maintenance of temperature in the region of normothermia (37°C) is the target in all TBI patients admitted to SRFT ICU. As a result, a stepwise cooling protocol is instituted in the event of a raised temperature. Prior to the onset of this study a 4-level cooling protocol was used in all neurosurgical patients. For this study the cooling protocol was modified, along with the ICU team, to ensure cooling was as efficient and streamlined as possible, using the methods available.

Once $T_{\text{brain}}$ or $T_{\text{rectal}}$ exceeded 38°C for more than 30 minutes, a cooling protocol was initiated. Table 1 describes each level of the protocol and Figure 1 demonstrates the stepwise nature of the protocol. In summary, once the protocol is initiated all patients received level 1 cooling. They then immediately receive either level 2 or 3 cooling, depending on whether the patient is receiving NMB for reasons other than whole body cooling. Level 2 or 3 cooling continues for a maximum of 5 hours or until $T_{\text{brain}} \leq 37°C$. If at the end of 5 hours $T_{\text{brain}}$ remained $\geq 37.5°C$ level 4 cooling is introduced. Again, this continues for a maximum of 5 hours or until $T_{\text{brain}} \leq 37°C$. 


Table 1 A description of each cooling level from the cooling protocol

<table>
<thead>
<tr>
<th>Level of Cooling</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1g of paracetamol was given every 4 hours until the cooling episode was completed, unless otherwise indicated by medical staff</td>
</tr>
<tr>
<td>2</td>
<td>Sheets/pillow-cases soaked (in hand hot water) were placed over the patient from chest to mid-thigh The soaks were renewed every hour or when they had begun to dry out The wet soaks could not be covered with dry sheets This level was continued for a maximum of 5 hours only</td>
</tr>
<tr>
<td>3</td>
<td>The patient required NMB for clinical reasons (as decided by ICU team) Soaked sheets/pillow-cases (in hand-hot water) were placed over the patient from chest to mid-thigh The soaks were renewed every hour or when they began to dry out The wet soaks could not be covered with dry sheets This level was continued for a maximum of five hours only</td>
</tr>
<tr>
<td>4</td>
<td>If a patient was progressing from level 2 cooling to level 4 cooling, NMB was necessary and therefore medical input was required If progressing from level 3 cooling to level 4 cooling the patient needed to continue on NMB The patient continued to be covered with wet soaks as outlined above in level 2 and 3 Insulin and nasogastric feed were stopped and the patient’s stomach aspirated via a nasogastric tube 500ml of iced water were passed into the stomach via the nasogastric tube The residual volume was aspirated after 10min This process was repeated every 15min Blood sugar was checked hourly Level 4 was continued for a maximum of five hours Once completed the nasogastric feed and insulin were recommenced as per ICU protocol. The need for NMB following level 4 cooling was discussed with the medical staff If $T_{brain/rectal}$ remained $\geq 37.5^\circ C$ medical advice was sought</td>
</tr>
</tbody>
</table>
Commence Level 1 Cooling

Is patient receiving NMB?

Yes

Commence Level 2 Cooling

No

Commence Level 3 Cooling

Continue to cool for a maximum of 5 hours or until $T_{\text{brain/rectal}} \leq 37^\circ C$

After 5 hours is $T_{\text{brain/rectal}} \geq 37.5^\circ C$?

No

No further cooling required

Yes

Commence Level 4 cooling; Continue Level 1 & 3 cooling

Continue until $T_{\text{brain/rectal}} \leq 37^\circ C$ or for a maximum of 5 hours

After 5 hours is $T_{\text{brain/rectal}} \geq 37.5^\circ C$?

No

No further cooling required

Yes

Seek medical advice
2.1.3 Outcome

An outcome score at 3 months following injury is determined for all TBI patients admitted to SRFT ICU the Glasgow Outcome Scale (GOS) (Appendix E). This score is determined by a member of the neurosurgical registrar team analysing outcome in all TBI patients admitted to ICU, as part of an ongoing prospective head injury audit analysing transfer times of these patients to SRFT. When possible the neurosurgical registrar makes a direct assessment of the patient. If the patient is in a peripheral hospital, contact is made with an appropriate member of the medical team and an assessment obtained. If the patient is at home, contact is made with the General Practitioner to ascertain that the patient is well. The patient or carer is then contacted directly via telephone and an assessment performed.
2.2 Patient Review

Approval was sought from the ICU and Neurosurgical teams prior to the onset of this patient review.

2.2.1 Patients

All patients with a severe TBI admitted within 24 hours of their injury to SRFT ICU during a one-year period (1\textsuperscript{st} March 2005 to 28\textsuperscript{th} February 2006) are included. The small cohort of patients, forming the observational study, was also recruited during this time period. Subjects are identified from an ICU admission database, which is accurately maintained by the medical staff at the time each patient is admitted.

2.2.2 Data Collection

Retrieval of Clinical Records

Once the subjects had been identified, their details were forwarded to the medical records department and their clinical notes retrieved once available. It was not possible to retrieve all of the identified clinical notes due to a number of factors including:

- Inability to trace
- In use by the coroner or legal team
- Inability to trace all of the required volumes of clinical notes

Information Collection

The researcher and a research assistant reviewed the medical notes and gathered the following information from the medical and nursing documentation:

- Patient demographics
- Date and time of injury
- Date and time of admission to Hope Hospital ICU
- Mechanism of injury
- Initial GCS
• Injuries sustained including CTB report

Information was then sought from the clinical notes at three specific time points:

1. Admission to ICU – The earliest temperature recorded in the nursing charts along with the method of temperature measurement was noted.

2. 48 Hours following Injury - No further information was sought at this time point for patients who died or were discharged from ICU before 48 hours from injury. If the patient remained on ICU the highest (peak) temperature recorded in the hourly nursing records was noted, along with the method of temperature measurement. At this stage the nursing charts were again reviewed and the number of documented hourly temperatures (length of time (LoT)) of ≥38°C (irrespective of method of temperature measurement) was recorded.

3. 120 Hours following Injury - No further information was sought at this time point for patients who died or were discharged from ICU before 120 hours from injury. The same information was recorded as for 48 hours from injury.

This information was recorded on a proforma. Once the proforma was completed the clinical notes were returned to medical records.

Additional Information

Once the data collection was complete, anatomical scoring of the injuries sustained by each patient was undertaken. A research assistant, trained in anatomical scoring by TARN, performed this. It consisted of assigning an Abbreviated Injury Scale (AIS) score to each injury sustained. A booklet (AIS90) of injuries along with their AIS score is available through TARN. Once an AIS score was allocated to each injury a patient had sustained, an Injury Severity Score (ISS) was calculated. The ISS score is determined by adding together the square of the highest AIS scores in three different body regions.

Missing Data

One set of notes was excluded from the patient review due to incomplete temperature recordings. Three other case notes were excluded from the review as the time of injury could not be ascertained.
2.2.3 Analysis of Results

Admission temperature and peak temperature at 48 and 120 hours from injury were analysed along with outcome using logistic regression. Due to some evidence that extremes of temperature may be harmful the results were also analysed for a potential quadratic relationship.

The LoT temperature was ≥38°C at 48 and 120 hours from injury were analysed along with outcome using logistic regression. Due to the skewed nature of LoT, these figures were transformed towards normality and reassessed with outcome using logistic regression.

In the event of a significant relationship or a relationship that tended towards significance, a graph demonstrating the modelled probability of death and temperature or LoT was plotted.
2.3 Observational Study

2.3.1 Ethical Approval

The observational study protocol was approved by the Tameside NHS Trust Local Research Ethics Committee (LREC) and the University of Manchester Research Ethics Committee. When necessary, protocol amendments also received approval from the Tameside LREC. All procedures, including recruitment of patients, were carried out in accordance with the Declaration of Helsinki and European Union guidelines describing good clinical practice.

2.3.2 Patients

All patients with a severe TBI who did not require immediate surgical intervention were considered for this observational study. Patients were recruited for a maximum of five days.

*Eligibility*

*Inclusion Criteria*
- Patients admitted to ICU for medical management of their severe blunt traumatic brain injury.
- Sedated, intubated and ventilated
  - All patients with a severe head injury (GCS ≤8) according to NICE guidelines require intubation
  - For any whole body cooling to occur the patient must be adequately sedated
- ≥16 years of age
- Within 24 hours of injury
  - To ensure that patients were enrolled into the study within a consistent time frame
  - Delays in patient transfer can be significant due to the high demand for intensive care beds
- Brain temperature and ICP monitoring
  - Most neurosurgical patients admitted to ICU required ICP monitoring, as ICP is difficult to determine in sedated, ventilated patients
  - In the majority of neurosurgical patients an ICP probe was sufficient. In patients with severe TBI not requiring immediate surgical intervention a dual monitoring device, which measured both ICP and $T_{brain}$ was inserted
**Exclusion Criteria**

- Patients requiring immediate surgical intervention
- Severe injury to other body region
- Pregnancy
- Pre-existing endocrine dysfunction

**Assent**

All patients eligible for this study were unconscious on admission to the neurosurgical ICU and informed consent was therefore not possible. Instead, once a patient was considered eligible for the study, informed assent was sought from the next of kin, as soon as was feasible following admission. The researcher approached the next of kin once the neurosurgical and intensive care teams had fully explained the condition of their relative and the monitoring and treatment modalities that were required. The researcher then explained the study in detail and the next of kin were given a period of time to read the accompanying study information leaflet (Appendix F) and reflect on the information given. Assent was only obtained if the next of kin or close family member was satisfied that their relative would want to take part in the study. No patients were recruited without assent from a close family member.

**2.3.3 Temperature/ICP Measurement**

All patients admitted to the observational study had a combined intracranial pressure-temperature sensor inserted. These catheters were inserted by one of the neurosurgical team, once the patient was admitted to ICU.

The monitoring kit used in SRFT is manufactured by Integra Neurosciences, Andover, UK (Camino intracranial pressure-temperature monitoring kit model 110-4BT). The dual intracranial pressure-temperature sensor was inserted as directed by the manufacturer. (See Appendix G for components; Appendix H for manufacturer insertion instructions)
$T_{\text{brain}}$ was continuously displayed on a Camino multi-parameter monitor. A numerical value and waveform of ICP was displayed continuously via a bedside monitoring system.

Using this system ICP is measured using a fibre optic device consisting of four fibres. Light is transmitted down one fibre (sender) from an LED source. The light is reflected off the polished walls of a mechanical bellows and collected by another fibre (receiver). The reflected light (signal) is collected by a photo-detector. The other pair of fibres are similarly mounted and exposed to the same light source but the light is not reflected off the polished bellows surface. The light is instead looped around from the sender back to the receiver. The light from the dummy path (reference) is compared to the signal forming a ratio. The transducer has a close to linear response for the pressure range of –20 to 300mmHg. The catheter needs to be linearised in order to get the required resolution from the transducer. This is achieved by applying a known pressure to the catheter during manufacture and recording the output pressure. This is used to construct a look-up table that the microprocessor in the multi-parameter monitor uses to correct the pressure. The ratio of light reflected from the bellows displacement to the reference is not the same for all transducers. In order to normalise the output, the transducer responses are rescaled so that the output to displacement ratio was the same for all transducers.

Intracranial temperature is measured by an electrically isolated thermodilution style thermistor. It is placed directly behind the bellows region of the catheter. Variation is linear over the region of 30 - 40°C.

The fibre optic pressure transducer has an accuracy of ±1mmHg and the thermistor transducer ±0.3°C.

$T_{\text{rectal}}$ was also recorded along with $T_{\text{brain}}$ in the sub group of patients recruited to the observational study. In all other TBI patients $T_{\text{rectal}}$ was the temperature measurement.
method of first choice. Tympanic temperature were measured and recorded only if $T_{\text{brain/rectal}}$ was not available.

### 2.3.4 Daily Review

All patients recruited were studied for a maximum of five days from the time of injury. At the time of recruitment baseline clinical details were collected. A daily morning review was also carried out and details collected. All physiological parameters recorded via the bedside acquisition monitor were retrieved for each patient during the recruitment period. In addition, the hourly records maintained by the nursing staff were copied on a daily basis. Additional information retrieved from the nursing hourly records included; medication infusion rates, sedation scores, GCS and pupil size and reactivity.

### 2.3.5 Cooling Episodes

In the event of a raised $T_{\text{brain}} \geq 38^\circ\text{C}$ for more than 30 minutes the cooling protocol, as outlined in 2.1.2, is initiated. A maximum of two cooling levels (or cooling episodes) were studied in each recruited patients.

During each studied cooling episode the researcher was present at the bedside to carry out observations and to ensure that the cooling did not deviate from protocol. In addition to the parameters recorded by the nursing staff and via the bedside acquisition monitor, the researcher recorded physiological parameters and medication infusion rates every 5 minutes. Any other observed patient changes or interventions by the treating physicians were also noted.

**BIS**

During studied cooling episodes only, BIS monitoring was performed. Fifteen minutes prior to the onset of cooling the BIS monitor was set up and a BIS sensor applied to the forehead of the patient. Once set up a BIS value is continuously displayed on the monitor screen and is
updated every 1 second. Full details of BIS equipment and the set up methods are available in Appendix I. The BIS value and signal quality were recorded by the researcher on a five-minute basis until completion of the studied cooling episodes.

Once BIS monitoring is commenced at the bedside, one channel of either the right or left frontal-temporal EEG montage is detected. EMG activity of the face/forehead is also incorporated. The EEG signal is detected, filtered and digitized within the Digital Signal Converter (DSC). High and low frequency artefacts are eliminated. The EEG signal is then divided into two-second segments. Statistical analysis (fast fourier transformation) and signal processing (power spectral and bispectral analysis) techniques are applied to the EEG segments. Power spectral analysis determines the relative proportions of the four basic EEG waveforms. Bispectral analysis identifies the beta ratio or proportion of EEG activity with a frequency greater than 13 cycles per second. Increased beta activity corresponds with the initial stages of sedation. Bispectral analysis also determines the relative synchrony of fast (beta) and slow (theta and delta) wave activity or the SynchFastSlow component of the BIS index. The SynchFastSlow component corresponds with moderate sedation or light anaesthetic states. The near suppression component is evaluated and consists of low amplitude/low frequency activity, associated with very deep anaesthetic states. The level of EEG suppression, in keeping with very deep anaesthetic states, is also determined. The combination of these EEG features is then used to determine the BIS index. Additional BIS monitoring parameters available, DSC specifications and EEG specifications are demonstrated in Appendix J.

2.3.6 Blood sampling

Blood sampling is carried out via an arterial line in all patients in ICU. Before the start of this study, the researcher was assessed in arterial line sampling and competency ensured.
During sampling the ICU arterial line blood sampling protocol is followed (Appendix K). For each of the five days a patient was enrolled in the study blood sampling was carried out every 12 hours (08:00 and 20:00). During studied cooling episodes blood sampling was performed 15 minutes before, followed by samples at 30, 180 and 300 minutes following the onset of cooling. All samples were analysed for S100b, IL-6 and TNF-α.

A maximum of 5mls of blood was sampled from the arterial port at these sampling times and transferred to a GEL biochemistry specimen bottle. The samples were taken to the biochemistry laboratory where the specimens were centrifuged at 3000rpm for 10 minutes and the serum then placed into a freezer and stored at -20˚C. These samples were transferred to a -70˚C freezer at the first available opportunity. They remained frozen at -70˚C until transport was arranged for these frozen samples to be dispatched to Kings College Hospital, London (Dr. R. Sherwood, Department of Clinical Biochemistry) for analysis of S100b, IL-6 and TNF- α. Transport was arranged via a courier company experienced in transporting frozen biological specimens. On the day of transfer the specimens were packed in dry ice and placed in an insulated polystyrene box. The transport company ensured the samples remained frozen until delivery to Kings College Hospital, London.

**S100b Analysis**

S100b is analysed on a Liaison chemiluminescence analyser (Diasorin, Berkshire, U.K.). The samples were removed from the -70°C freezer and thawed before analysis.

Two trigger solutions are injected into wells by a luminometer. Trigger 1 solution contains alkaline peroxide and trigger 2 a catalyst solution. These solutions oxidise an isoluminol derivative bound to a magnetic particle. The oxidised product is in an excited state and the subsequent return to ground state results in emission of blue light (420-430 nm), which is quantified in three seconds and expressed in relative light units (RLU) by the integrated system luminometer.
For the measurement of S100b in human serum the assay is a two-site chemiluminescence immunoassay. It utilises paramagnetic particles coated with two mouse monoclonal antibodies to human S100b and one mouse monoclonal antibody labelled with an isoluminol derivative. S100b is sandwiched between these antibodies.

The sample containing S-100b, the magnetic particles and buffer is incubated for a period of time then; the unbound magnetic particles are removed by a wash cycle. The isoluminol labelled antibody is then added and after a second incubation the unbound labelled antibody is removed by a second wash cycle. The formation of a soluble sandwich complex occurs only in the presence of S-100b molecules, which bridge the two antibodies. Therefore, only peptides that bridge these two antibodies can be quantitated (Fig. 2).

The wells containing the washed magnetic particles are transported into the system luminometer, which automatically injects trigger 1 and trigger 2 solutions and initiates the chemiluminescence reaction. The light is quantitated by the luminometer and expressed as RLU. The amount of bound labelled antibody is directly proportional to the concentration of S-100β in the sample.

The minimal detectable dose of S100b was 0.02µg/l. The intra- and inter-assay precisions for S100β from the Department of Clinical Biochemistry, Kings College Hospital, London, are given in Appendix L.
**TNF-α Analysis**

TNF-α is analysed using a Quantikine HS TNFα ELISA kit (R & D Systems Europe, Abingdon, U.K.).

This assay employs the quantitative sandwich enzyme linked immunoassay (ELISA) technique. A monoclonal antibody specific for TNF-α is pre-coated onto a microplate. Standards and samples are pipetted into the wells of the microplate and the immobilised antibody binds any TNF-α present. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for TNF-α is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells. Following incubation, an amplifier solution is added to the wells and colour develops in proportion to the amount of TNF-α bound in the initial step. The colour development is stopped and the intensity of the colour is measured.
This TNF-α HS immunoassay kit used an amplification system in which the alkaline phosphatase reaction provides a cofactor that activates a redox cycle leading to the formation of a coloured product. In this amplification system, alkaline phosphatase dephosphorylates the reduced form of nicotinamide adenine dinucleotide phosphate, NADPH (substrate), to reduced nicotinamide adenine dinucleotide, NADH. The NADH subsequently serves as a specific cofactor that activates a redox cycle driven by the secondary enzyme system consisting of alcohol dehydrogenase and diaphorase (amplifier). In the reaction catalysed by diaphorase, NADH reduces a tetrazolium salt (INT-violet or iodonitrotetrazolium violet) to produce an intensely coloured formazan dye and NAD\(^+\). NAD\(^+\) in turn is reduced by ethanol, in an alcohol dehydrogenase-catalysed reaction, to regenerate NADH, which can then re-enter the redox cycle. The rate of reduction of the tetrazolium salt and thus the amount of coloured product formed are directly proportional to the amount of TNF-α bound in the initial step.

The minimal detectable dose of TNF-α is 0.12pg/ml\(^{-1}\). The intra- and inter-assay precisions for TNF-α from the Department of Clinical Biochemistry, King's College Hospital, London, are given in Appendix L.

**IL-6 Analysis**

IL-6 is analysed using a Quantikine HS IL-6 ELISA kit (R & D Systems Europe, Oxon, UK). This method also employs the quantitative sandwich ELISA technique. The methods used to detect IL-6 by this kit are as described for TNF-α, but using monoclonal antibodies and enzyme-linked polyclonal antibodies specific for IL-6.

The minimal detectable dose of IL-6 is 0.039pg/ml. The intra- and inter-assay precisions IL-6 from the Department of Clinical Biochemistry, King's College Hospital, London, are given in Appendix L.
2.3.7 Statistical Analysis

Due to the nature of this observational study no statistical analysis has been performed on the results obtained.
Chapter 3

Results
In this chapter the results of the two studies are described. The results of the patient review study have been tabulated and where appropriate displayed graphically. The results of the observational study are mainly displayed in graphical form for individual patients.

3.1 Patient Review

3.1.1 Case Notes Retrieved

In a 12 month period 72 patients were admitted to SRFT ICU either via SRFT A&E or transfer from a district hospital. Eleven sets of notes could not be retrieved or only incomplete volumes were available with inadequate information. Once retrieved a further 4 sets of notes were excluded due to either incomplete temperature recordings or lack of information regarding the time of injury (Fig 3).
Fig. 3 Flow chart demonstrating the case notes excluded from the patient review
3.1.2 Admission

Patients

A total of 57 patients were included in the patient review and each had a documented admission temperature. A high proportion of admission temperature readings are tympanic as the first temperature reading is commonly taken before rectal and brain temperature probes have been inserted.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of case notes audited</td>
<td>57</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
</tr>
<tr>
<td>Age (years) (median/range)</td>
<td>33 (17 to 76)</td>
</tr>
<tr>
<td>Admission to ICU delay (hours from injury) (median/range)</td>
<td>8 (3 to 24)</td>
</tr>
<tr>
<td>GCS (median/range)</td>
<td>7 (3 to 15)</td>
</tr>
<tr>
<td>AIS (head) (median/range)</td>
<td>4 (3 to 5)</td>
</tr>
<tr>
<td>ISS (median /range)</td>
<td>25 (10 to 45)</td>
</tr>
<tr>
<td>Admission temperature (°C)† (median/range)</td>
<td>36.4 (33 to 39.6)</td>
</tr>
</tbody>
</table>

Table 2 Patient Demographics for admission temperature
†Method of temperature measurement - 77% tympanic, 14% brain, 9% rectal

Admission Temperature

Median admission temperature was 36.4°C (range 33 to 39.6°C). Admission temperature was measured using tympanic readings in 77%, brain in 14% and rectal in 9% of patients. The distribution of admission temperature in survivors and non-survivors is shown in Fig. 4.
Fig. 4 Distribution of admission temperature in survivors (n=43) and non-survivors (n=14)

**Analysis of Admission Temperature and Outcome**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (Confidence Interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission Temperature</td>
<td>0.63 (0.39 to 1.06)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Table 3 Logistic regression analysis results of admission temperature and outcome

There was no evidence of a quadratic relationship between admission temperature and outcome when a quadratic model was applied.
3.1.3 48 Hours following Injury

**Patients**

A total of 6 patients died or were discharged from ICU within 48 hours of their injury and were not included in the analysis at this time point. Although the proportion of rectal and brain temperature measurements have increased since admission temperature, a significant proportion of patients continued to have tympanic temperature readings, even though local TBI policy indicates $T_{\text{rectal}}$ should be routinely monitored.
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of case notes audited†</td>
<td>51</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>43</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
</tr>
<tr>
<td>Age (years) (median/range)</td>
<td>37 (17 to 76)</td>
</tr>
<tr>
<td>Peak temperature (°C) ‡ (median/range)</td>
<td>38 (33.9 to 39.1)</td>
</tr>
<tr>
<td>Length of time temperature ≥38°C (hours)</td>
<td>1.1(0 to 23)</td>
</tr>
<tr>
<td>Length of time temperature ≥38°C (hours)</td>
<td>1.1(0 to 23)</td>
</tr>
</tbody>
</table>

Table 4 Patient demographics 48 hours following injury
†Exclusions – 3 patients discharged from ICU and 3 patients died <48 hours from injury
‡ Method of temperature measurement – 35% brain, 37% tympanic, 28% rectal

**Peak Temperature 48 Hours following Injury**

The median peak temperature was similar in both survivors (38°C) and non-survivors (38.1°C). The distribution of peak temperature in survivors and non-survivors is demonstrated in Fig. 6.
Fig. 6 Distribution of peak temperature 48 hours following injury in survivors (n=40) and non-survivors (n=11).

Analysis of Peak Temperature in the 48 hours following injury and Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (Confidence Interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Temperature 48 hours following Injury</td>
<td>1.03 (0.46 to 2.3)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Table 5 Logistic regression analysis results of peak temperature 48 hours following injury and outcome

There was no evidence of a quadratic relationship between peak temperature 48 hours following injury and outcome when a quadratic model was applied.
LoT Temperature ≥38°C in the 48 Hours following Injury

There was no difference in the median LoT temperature was ≥38°C in survivors and non-survivors 48 hours following injury. The distribution of LoT is demonstrated in Fig. 7.

Fig. 7 LoT temperature ≥38°C in the 48 hours following injury in survivors (n=40) and non-survivors (n=11)

Analysis of LoT temperature ≥38°C in the 48 hours following Injury and Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LoT Temperature ≥38°C in the 48 hours following Injury</td>
<td>1.03 (0.92 to 1.1)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Table 6 Logistic regression analysis results of LoT temperature ≥38°C in the 48 hours following injury and outcome
When LoT was transformed towards normality and re-assessed the results were not substantively different.

### 3.1.4 120 Hours following Injury

**Patients**

A further 15 patients had been discharged from ICU and 3 patients had died within 120 hours of their injury and were not analysed at this time point. A considerable proportion of patients continued to have tympanic temperature monitoring. Patient demographics for this time point are demonstrated in Table 7.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of case notes audited†</td>
<td>33</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
</tr>
<tr>
<td>Age (years) (median/range)</td>
<td>33 (17-67)</td>
</tr>
<tr>
<td>Peak temperature (°C)‡ (median/range)</td>
<td>38.7 (36.8-40.1)</td>
</tr>
<tr>
<td>Length of time temperature ≥38°C (hours) (median/range)</td>
<td>10 (0-57)</td>
</tr>
</tbody>
</table>

Table 7 Patient demographics 120 hours following injury

† Exclusions – 15 patients discharged from ICU and 3 patients died
‡ Method of temperature measurement – 36% brain, 42% tympanic, 21% rectal

**Peak Temperature 120 Hours following Injury**

The median peak temperature was higher in survivors (38.6°C) than in non-survivors (38.1°C). The distribution of peak temperature in survivors and non-survivors is demonstrated in Fig. 8.
Fig. 8 Distribution of peak temperature in the 120 hours following injury in survivors (n=25) and non-survivors (n=8)

Analysis of Peak Temperature in the 120 hours following Injury in Survivors and Non-Survivors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Temperature in the 120 hours following Injury</td>
<td>0.26 (0.07 to 0.96)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Table 8 Logistic Regression analysis results of peak temperature in the 120 hours following injury and outcome

There was no evidence of a quadratic relationship between peak temperature 120 hours following injury and outcome when a quadratic model was applied.
**Modelled Probability of Death for Individual Patients Based on Logistic Regression Results of Outcome and Peak Temperature 120 hours from Injury**

![Graph showing modelled probability of death for patients based on logistic regression analysis of outcome and peak temperature 120 hours from injury.](image)

Fig. 9 Modelled probability of death for each patient reviewed based on logistic regression analysis of outcome and peak temperature 120 hours from injury.

**LoT Temperature $\geq 38^\circ C$ in the 120 Hours following Injury**

The median LoT temperature was $\geq 38^\circ C$ in the 120 hours following injury was greater in survivors (12 hours) than non-survivors (5 hours). The distribution of LoT in survivors and non-survivors is demonstrated in Fig. 10.
Fig. 10 LoT temperature $\geq 38^\circ$C in the 120 hours following injury in survivors (n=25) and non-survivors (n=8)

**Analysis of LoT temperature $\geq 38^\circ$C in the 120 hours following injury and Outcome**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LoT Temperature $\geq 38^\circ$C in the 120 hours following Injury</td>
<td>0.95 (0.88 to 1.02)</td>
<td>0.17</td>
</tr>
<tr>
<td>$\sqrt{\text{LoT Temperature}} \geq 38^\circ$C in the 120 hours following Injury</td>
<td>0.7 (0.46 to 1.06)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Table 9 Logistic regression analysis results of LoT and $\sqrt{\text{LoT}}$ temperature $\geq 38^\circ$C in the 120 hours following injury and outcome
Fig. 11 Modelled probability of death for each patient reviewed, based on logistic regression analysis of outcome and √LoT temperature ≥38°C in the 120 hours from injury

### 3.1.5 Summary

**Admission Temperature**

On examination of admission temperatures, the median admission temperature was higher in the group of survivors (36.5°C) when compared to the group of non-survivors (36°C).

Analysis with logistic regression suggested an approximately 40% reduction in the odds of death with each degree rise in admission temperature. With a P-value of 0.08 the results only tended towards significance. When a quadratic model was applied the results were not significant.

**48 Hours from Injury**

There was little difference in the median peak temperature values between the survivors (38°C) and non-survivors (38.1°C). Analysis of peak temperature and outcome did not
demonstrate a significant relationship. Again, no significant relationship was found when a quadratic model was applied.

When the LoT temperature was ≥38°C was considered, there was no difference in the median LoT between the two groups of patients. Analysis with logistic regression did not demonstrate a significant relationship. This was also the case when the figures were transformed towards normality.

120 hours from Injury

The median peak temperature in the group of survivors (38.6°C) was higher than the group of non-survivors (38.1°C). Analysis using logistic regression demonstrated an approximately 75% reduction in the odds of death with each degree rise in peak temperature. The results were not significant when a quadratic model was applied.

On review of LoT temperature was ≥38°C, the median LoT was higher in the survivors (12 hours) when compared to the non-survivors (5 hours). Analysis with logistic regression did not reveal a significant relationship. However, when the figures were transformed towards normality the results tended towards significance, suggesting a possible relationship between LoT and outcome.
3.2 Observational Study

3.2.1 Patients

Eight patients were recruited to the observational study. A summary of patient demographics is given in Table 10.

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Sex (M/F)</th>
<th>Age (years)</th>
<th>First Documented GCS</th>
<th>Mechanism of injury†</th>
<th>Abbreviated Injury Scale Score (AIS)</th>
<th>Injury Severity Score (ISS)</th>
<th>Glasgow Outcome Score (GOS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>25</td>
<td>9</td>
<td>Fall from a bridge</td>
<td>4</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>25</td>
<td>10</td>
<td>Fall down steps</td>
<td>4</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>42</td>
<td>7</td>
<td>Assault</td>
<td>4</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>25</td>
<td>9</td>
<td>Fall from balcony</td>
<td>4</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>58</td>
<td>7</td>
<td>RTA†</td>
<td>4</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>61</td>
<td>5</td>
<td>RTA</td>
<td>3</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>18</td>
<td>5</td>
<td>RTA</td>
<td>4</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>18</td>
<td>6</td>
<td>RTA</td>
<td>4</td>
<td>17</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 10 Patient Demographics for the Observational Study

† - For further details of injury mechanism and injuries sustained see Appendix M
‡ - Road Traffic Accident

Patient 6 had a serious TBI, while all other patients recruited had a severe TBI as classified by AIS. The ISS reflects the exclusion of patients with severe multi-system trauma.

Each patient recruited had a varying course on ICU. Table 11 demonstrates the differences in admission times and ICU stay. It also illustrates the period of recruitment and minimum and maximum $T_{\text{brain}}$ during this period. All recruited patients were admitted within 12 hours of their injury.
Table 11 Summary of patient ICU admission, study period and ICU stay and maximum and minimum $T_{\text{brain}}$ during the study period

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Admission to ICU (Hrs from Injury)</th>
<th>ICU Stay† (Hrs from Injury)</th>
<th>Recruitment Period (Hrs from Injury)</th>
<th>% Time $T_{\text{brain}} \geq 38^\circ C$</th>
<th>$T_{\text{brain}}$ Max (°C) ‡</th>
<th>$T_{\text{brain}}$ Min (°C) ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>205</td>
<td>120</td>
<td>15</td>
<td>38.9</td>
<td>36.2</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>168</td>
<td>136.5</td>
<td>16</td>
<td>38.4</td>
<td>34.5</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>121</td>
<td>120</td>
<td>5</td>
<td>38.3</td>
<td>34.3</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>546</td>
<td>125</td>
<td>16</td>
<td>38.5</td>
<td>36.3</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>336</td>
<td>142</td>
<td>43</td>
<td>40.0</td>
<td>35.9</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>208</td>
<td>120</td>
<td>26</td>
<td>38.4</td>
<td>36.4</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>116</td>
<td>115</td>
<td>23</td>
<td>39.0</td>
<td>34.8</td>
</tr>
<tr>
<td>8</td>
<td>6.5</td>
<td>507</td>
<td>120.5</td>
<td>15</td>
<td>38.6</td>
<td>35.0</td>
</tr>
</tbody>
</table>

† Discharge to level 2 care or death
‡ Maximum and minimum $T_{\text{brain}}$ during the recruitment period

3.2.2 Temperature Measurement

In the small cohort of patients recruited for this observational study, $T_{\text{brain}}$ was the temperature measurement of first choice. In addition $T_{\text{rectal}}$ was measured in seven of the eight recruited patients. Table 12 demonstrates median $T_{\text{brain}}$ and $T_{\text{rectal}}$ temperature for each patient during the study period, except for patient 7 in whom $T_{\text{rectal}}$ monitoring was not performed.

The median values of $T_{\text{brain}}$ and $T_{\text{rectal}}$ were mostly within generally accepted normothermic ranges. On closer inspection, although there were few recorded extremes of temperature, most patients experienced a wide range of $T_{\text{brain}}$ during the studied periods (Minimum recorded $T_{\text{brain}}$ – 34.3°C; maximum recorded $T_{\text{brain}}$ - 40°C. The median differences between $T_{\text{brain}}$ and $T_{\text{rectal}}$ were small and within the limits of accuracy of both probes in most patients. There was a tendency for $T_{\text{brain}}$ to be slightly higher than $T_{\text{rectal}}$. One exception to this was patient 6, who demonstrated a $T_{\text{rectal}}$ greater than $T_{\text{brain}}$ for a significant proportion of the study period. Although the median values are relatively close it is important to note that this
masks potentially significant differences (up to 1.4°C) at specific time points. It is difficult to predict if and when these large differences will occur but, these large differences do demonstrate the potential problems that can arise using indirect measurements of $T_{\text{brain}}$.

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>$T_{\text{brain}}$ (°C) Median (range)</th>
<th>$T_{\text{rectal}}$ (°C) Median (range)</th>
<th>$T_{\text{brain}}$-$T_{\text{rectal}}$ (°C) Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37.4 (36.2-38.9)</td>
<td>37.1 (36-38.5)</td>
<td>0.1 (-0.1 to 0.9)</td>
</tr>
<tr>
<td>2</td>
<td>37.1 (34.5-38.4)</td>
<td>37 (35-38.3)</td>
<td>0.1 (-0.7 to 0.8)</td>
</tr>
<tr>
<td>3</td>
<td>37 (34.3-38.3)</td>
<td>36.9 (34.4-38.2)</td>
<td>0.1 (-0.7 to 0.6)</td>
</tr>
<tr>
<td>4</td>
<td>37.1 (36.3-38.5)</td>
<td>36.9 (34.8-38.3)</td>
<td>0.2 (0.1 to 0.7)</td>
</tr>
<tr>
<td>5</td>
<td>37.85 (35.9-40)</td>
<td>37.5 (35.9-38.6)</td>
<td>0.4 (-0.1 to 1.3)</td>
</tr>
<tr>
<td>6</td>
<td>37.3 (36.4-38.4)</td>
<td>38.1 (37-39.3)</td>
<td>-0.6 (-1.4 to 0.7)</td>
</tr>
<tr>
<td>7</td>
<td>37.1 (34.8-39)</td>
<td>None available</td>
<td>None available</td>
</tr>
<tr>
<td>8</td>
<td>37 (35-38.6)</td>
<td>36.5 (35.3-38.6)</td>
<td>0.1 (-0.9 to 0.7)</td>
</tr>
</tbody>
</table>

Table 12 $T_{\text{brain}}$ and $T_{\text{rectal}}$ (median/range) and the median difference for each studied patient

### 3.2.3 Delivery of Cooling Interventions to Maintain Normothermia

Seven out of the eight patients recruited had temperature reduction methods delivered. Two of these patients did not have any delivered cooling episodes studied. A summary of cooling episodes delivered and studied is given in the Table 13.
<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Total Number of Cooling Episodes Delivered</th>
<th>Number of Cooling Episodes Studied</th>
<th>Reasons Cooling Episodes Not Studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>2†</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>2†</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>2†</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>2†</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>2†</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>0</td>
<td>Sedation off at times $T_{\text{brain}}&gt;38^\circ\text{C}$</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>0</td>
<td>Researcher unavailable due to clinical on-call</td>
</tr>
</tbody>
</table>

Table 13 Summary of cooling episodes delivered and studied
† Maximum number of cooling episodes studied as per protocol

*Delivery of Cooling Episodes throughout the Recruitment Period*

Individual graphs follow depicting the change in $T_{\text{brain}}$ with time over the recruitment period for each patient. Delivered and studied cooling episodes will be represented by a black dashed box, while delivered but not studied cooling episodes by a blue dashed box.
Patient 1 experienced a rise in $T_{\text{brain}}$ on admission to ICU, early following injury. During this time two cooling episodes (level 2 followed by level 4) were delivered and studied. $T_{\text{brain}}$ remained below 38°C until later in the study period. At 108 hours from injury an episode of level 2 cooling was required as a result of a raised $T_{\text{brain}}$. This was delivered over a ten-hour period, rather than the maximum five hours prescribed in the study protocol and despite a reduction in temperature to target levels within this 5 hour time frame.

Fig. 12 $T_{\text{brain}}$ during the recruitment period in Patient 1
Two episodes of cooling (level 2 and level 4) were required early following injury. Both of these episodes were studied. A further two episodes (level 2 and level 4) were delivered later in the study period but not studied. During these later episodes, level 2 cooling was delivered for the maximum 5 hours without an adequate reduction of $T_{\text{brain}}$. Indeed, there was a small rise in $T_{\text{brain}}$ at the end of 5 hours (37.3°C) in comparison to starting temperature (37.2°C). Level 4 cooling was commenced following this, as per protocol, and continued for 4 hours only, as temperature reduction targets were met. Outside these time periods there were two transient rises in $T_{\text{brain}}$ ($\geq 38^\circ\text{C}$) that did not require intervention and settled spontaneously.
Fig. 14 $T_{\text{brain}}$ during the recruitment period in Patient 3

Early following admission a level 2 cooling episode was delivered, even though $T_{\text{brain}}$ rose above 38°C only transiently. This cooling episode was not studied due to the deviation from protocol along with lack of assent. Over the next 34 hours, without any further attempts at temperature reduction, $T_{\text{brain}}$ continued to fall to a minimum of 34.3°C. During this period the patient received maximal medical therapy (barbiturate coma was commenced at 17 hours from injury) for a refractory ICP however, ICP continued to rise and the patient underwent an emergency decompressive craniectomy 52 hours following injury. On return from theatre $T_{\text{brain}}$ had returned to normothermic levels. In the post-operative period the patient developed two episodes of $T_{\text{brain}} \geq 38°C$ that did not settle spontaneously. Level 3 cooling was delivered and studied on both occasions.
Fig. 15 $T_{\text{brain}}$ during the recruitment period in Patient 4

Despite an initial rise in $T_{\text{brain}}$, that did not require any intervention, $T_{\text{brain}}$ did not rise above 38°C until 87 hours following injury. At this stage two episodes of cooling (level 3 and 4) were delivered and studied. From approximately 70 hours following injury there was increasing difficulty maintaining ICP and the need for barbiturate therapy coincided with this late rise in $T_{\text{brain}}$. Despite aggressive medical management to control ICP this patient required an emergency decompressive craniectomy. Following this procedure $T_{\text{rectal}}$ was measured as the $T_{\text{brain}}$ probe had been removed. There was a gradual rise in $T_{\text{rectal}}$ from a minimum of 35°C post surgery to a maximum of 38.3°C. No cooling episodes were delivered and $T_{\text{rectal}}$ remained $\geq 38°C$ for approximately 2.5 hours.
Patient 5

Fig. 16 $T_{\text{brain}}$ during the recruitment period in Patient 5

Hourly $T_{\text{brain}}$ has been demonstrated in Fig. 16, as a large proportion of $T_{\text{brain}}$ was not recorded due to an unrecognised problem with the patient bedside acquisition monitor. This subject did not remain sedated throughout the study period. Due to the nature of his injuries and his stable course, sedation was stopped at 25 hours following injury but was rapidly recommenced due to a rise in ICP. Sedation was again stopped at 53 hours from injury but was recommenced 12 hours later as a result of persistent low GCS and concerns regarding a rise in $T_{\text{brain}}$. His sedation was finally turned off at 98 hours following injury. During the study period two cooling episodes were delivered at times when sedation was switched off and as a result of deviation from protocol were not studied. These episodes also deviated from protocol as they exceeded the maximum length of time for a cooling level. Two further episodes of cooling delivered while the patient was sedated were studied.
As with patient 5, this patient did not remain sedated throughout the entire study period. Sedation was initially switched off at 32 hours following injury. It was recommenced for three hours at 55 hours from injury, for a procedure. Following this it remained switched off. Throughout most of the study period $T_{\text{brain}}$ remained below 38°C. From approx 70 hours from injury the patient experienced several spikes in $T_{\text{brain}} \geq 38^\circ$C that did not require intervention. The first episode of cooling (level 2) delivered, occurred not only when sedation was switched off but also when the starting temperature was $<38^\circ$C. It was also delivered for longer than dictated by protocol. By the end of this cooling episode $T_{\text{brain}}$ had increased to $\geq 38^\circ$C. A short time later a second level 2 cooling episode was delivered and at this stage $T_{\text{brain}}$ was $>39^\circ$C. Due to deviations from protocol neither of these cooling episodes was studied.
Sedation was switched off 58 hours following injury. Hourly $T_{\text{brain}}$ has also been represented in Fig. 18, to provide data for the periods of time $T_{\text{brain}}$ was not recorded via the patient bedside acquisition monitor. The patient was recruited for 115 hours following injury, however due to his improving clinical condition the $T_{\text{brain}}$ probe was removed at 86 hours from injury. At the time of removal $T_{\text{brain}}$ was 39°C. The patient experienced a $T_{\text{brain}} \geq 38^\circ\text{C}$ at 56 hours from injury and again at 77 hours from injury. This first rise lasted for six hours while the second lasted for 1.5 hours. No cooling episodes were delivered or studied as sedation was switched off.
Fig. 19 $T_{\text{brain}}$ during the recruitment period in Patient 8

Hourly $T_{\text{brain}}$ is also represented in Fig. 19 to provide data for the periods of time $T_{\text{brain}}$ was not recorded via the patient bedside acquisition monitor. During the early study period the patient did not experience any rises in temperature. Indeed, from approximately 20 hours to 65 hours from injury, $T_{\text{brain}}$ tended to be spontaneously between 35 and 36°C. From this point the temperature gradually increased and reached 38.5°C. At this stage a level 2 cooling episode was delivered. Although there was an initial decrease in temperature it rose again and level 4 cooling was commenced as a result of lack of temperature reduction. During this cooling period the temperature again fell initially but rose towards the end of the cooling episode. Two further cooling episodes were delivered following this despite the temperature being below levels at which cooling should be commenced. Due to clinical commitments a researcher was not present during these episodes. The first two cooling episodes delivered followed the devised protocol; however the final two episodes delivered deviated from protocol.
3.2.4 Studied Cooling Episodes

As already demonstrated five patients each had two episodes of cooling studied. Table 14 demonstrates $T_{\text{brain}}$ at the beginning and end of each studied cooling episode and the difference achieved over the cooling period.

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Cooling Episode</th>
<th>Level of Cooling</th>
<th>$T_{\text{brain}}$ Start ($^\circ$C)</th>
<th>$T_{\text{brain}}$ End ($^\circ$C)</th>
<th>$T_{\text{brain}}$ start-$T_{\text{brain}}$ end ($^\circ$C)</th>
<th>Length of Cooling (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>38.7</td>
<td>38.9</td>
<td>↑ -0.2</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4</td>
<td>38.8</td>
<td>37.1</td>
<td>↓ 1.7</td>
<td>300</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2</td>
<td>38.2</td>
<td>38.1</td>
<td>↓ 0.1</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4</td>
<td>38.3</td>
<td>37</td>
<td>↓ 1.3</td>
<td>265</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>3</td>
<td>38.4</td>
<td>37.2</td>
<td>↓ 1.2</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>38.1</td>
<td>37</td>
<td>↓ 1.1</td>
<td>300</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>3</td>
<td>38.4</td>
<td>38.2</td>
<td>↓ 0.2</td>
<td>215</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4</td>
<td>38.3</td>
<td>37.5</td>
<td>↓ 0.8</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>2</td>
<td>38.1</td>
<td>38</td>
<td>↓ 0.1</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4</td>
<td>38</td>
<td>37.2</td>
<td>↓ 0.8</td>
<td>130</td>
</tr>
</tbody>
</table>

Table 14 Summary of cooling episodes for patient 1-5 and changes in $T_{\text{brain}}$ during each episode studied

3.2.5 The Effect of Cooling on Brain Temperature

Changes in $T_{\text{brain}}$ during studied cooling episode will be described in more detail for each patient. The course of $T_{\text{brain}}$ over each cooling episode delivered and studied will also be graphically represented. An arrow will define the beginning and end of each cooling episode.
The temperature at which cooling was initiated (38°C) is depicted by a dashed black line, while the target temperature (37°C) by a solid black line.

**Patient 1**

Fig. 20 Change in $T_{\text{brain}}$ during level 2 and 4 cooling in Patient 1

Both episodes of cooling were delivered early following injury. Level 2 cooling was undertaken for five hours as per protocol. During this time the temperature did not fall below 38°C, and rose above the starting temperature in the early phase. At the end of five hours of level 2 cooling $T_{\text{brain}}$ was higher than at the beginning. Due to lack of temperature reduction level 4 cooling was initiated as per protocol. $T_{\text{brain}}$ reduced throughout this level and at the end of the five-hour cooling period was within target limits.
Level 2 cooling was initiated due an early rise in temperature following injury. Following an initial small fall, $T_{\text{brain}}$ then rose to a maximum of 38.6°C before falling to only 0.1°C below the starting temperature. As per protocol, the lack of temperature reduction at the end of five hours of level 2 cooling resulted in the initiation of level 4 cooling. In the initial phases of this level of cooling there was a small secondary rise in $T_{\text{brain}}$. $T_{\text{brain}}$ was successfully reduced to target temperature in 4.4 hours.
Fig. 22 Change in $T_{\text{brain}}$ during level 3 and level 3 cooling in Patient 3

The first studied episode of level 3 cooling was commenced at 68.5 hours from injury. There was a steady decrease in $T_{\text{brain}}$ and at the end of the study period the temperature was within target limits. A second episode of level 3 cooling was delivered and studied at 88 hours from injury. In the initial phase of cooling there were some fluctuations in temperature followed by a fall to target values. A thiopentone infusion was running before and during both studied cooling episodes.
During level 3 cooling $T_{\text{brain}}$ did not fall below 38°C and in the early phase actually rose above the starting temperature. As a result of the increasing difficulty controlling ICP and the lack of temperature reduction with level 3 cooling, the clinical team requested that level 3 cooling was converted to level 4 after 3.6 hours. Although $T_{\text{brain}}$ fell below 38°C and continued to fall during level 4 cooling, the continued deterioration in the patient’s condition led to this cooling episode being stopped after 1.2 hours. At this stage the patient was transferred to theatre for emergency surgery, in the form of a decompressive craniectomy. A thiopentone infusion was commenced shortly after level 3 cooling commenced and continued throughout the remainder of the cooling period.
Fig. 24 Change in $T_{\text{brain}}$ during level 2 and 4 cooling episodes in Patient 5

These two episodes of cooling were delivered late in the study period. During level 2 cooling the temperature initially rose above the starting temperature before falling to a minimum of 37.8°C. Prior to completion $T_{\text{brain}}$ rose again slightly and at the end of five hours was only 0.1°C below the starting temperature. Level 4 cooling was commenced and steadily reduced $T_{\text{brain}}$ to within target limits. The clinical team requested that level 4 cooling was stopped after only two hours due to a fall in serum sodium measurements and an unexpected rise in ICP. After two hours the temperature had been reduced from 38°C to 37.2°C.
Summary of $T_{\text{brain}}$ Changes during Studied Cooling Episodes

The above figure provides a summary of the change in $T_{\text{brain}}$ during all of the studied cooling episodes. The target temperature (37°C) is represented by a solid line, while the temperature at which cooling should be considered (38°C) is represented by a dashed black line.

Fig. 25 Changes in $T_{\text{brain}}$ during all studied cooling episodes
Any reduction in $T_{\text{brain}}$ achieved during the cooling episodes studied is accomplished at a slow rate (Fig. 26). On one occasion the temperature at the end of level 2 cooling was higher than the starting temperature and on two other occasions the temperature reduction and rate of reduction were negligible. Level 3 cooling achieved temperature reduction on all three occasions it was studied but again the reduction achieved and rate of reduction were lacking. Level 4 cooling, which appeared to be the most consistent level of cooling to reduce $T_{\text{brain}}$, has also demonstrated a slow rate of reduction. The maximum rate of reduction ($0.68^\circ\text{Chr}^{-1}$) achieved was a level 4 cooling in patient 4. During the other nine cooling episodes there was a range of reduction rates from 0.02 to $0.37^\circ\text{Chr}^{-1}$.
Summary

Each patient studied post TBI experienced a differing pattern and variable range of temperatures (34.3 to 40ºC). Each patient also underwent differing numbers and levels of cooling.

Three episodes of level 2 cooling were studied. In all cases there was a rise in T\textsubscript{brain} above the starting value and none of the three episodes of level 2 cooling resulted in reduction of a raised T\textsubscript{brain} to target levels. On one occasion the end temperature was higher than the start temperature while on the other two occasions temperature reduction was by only 0.1ºC.

There were also three episodes of level 3 cooling studied. In two of these three studied episodes target temperature reduction was reached. Both level 3 episodes were delivered to patient 3, late in the study period and following a decompressive craniectomy. The remaining level 3 episode studied was discontinued after 3.6 hours due to lack of temperature reduction in association with increasing ICP problems. During this period a reduction of only 0.2ºC had been achieved.

Four episodes of level 4 cooling were studied. On three occasions target temperatures were met. In one such episode the clinical team stopped level 4 cooling earlier than specified in the protocol, as a result of falling sodium levels and an unexpected rise in ICP. Target temperature was not achieved in one studied episode. On this occasion cooling was cut short, as the patient required emergency surgery due to spiralling ICP values.
3.2.6 The Effects of Cooling on Physiological Parameters

**ICP**

Table 15 demonstrates the ICP at the beginning and end of each cooling phase studied. It also illustrates the peak ICP during the cooling episodes and the percentage of time ICP ≥25mmHg.

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Level of Cooling (mmHg)</th>
<th>ICP&lt;sub&gt;start&lt;/sub&gt; (mmHg)</th>
<th>ICP&lt;sub&gt;end&lt;/sub&gt; (mmHg)</th>
<th>ICP&lt;sub&gt;end&lt;/sub&gt; – ICP&lt;sub&gt;start&lt;/sub&gt; (mmHg)</th>
<th>% time ICP≥25mmHg</th>
<th>Peak ICP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>10</td>
<td>20</td>
<td>↑10</td>
<td>5</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>17</td>
<td>20</td>
<td>↑3</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>16</td>
<td>28</td>
<td>↑12</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>13</td>
<td>18</td>
<td>↑5</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>31</td>
<td>25</td>
<td>↓6</td>
<td>98</td>
<td>31</td>
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<td></td>
<td>3</td>
<td>23</td>
<td>31</td>
<td>↑8</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>25</td>
<td>15</td>
<td>↓10</td>
<td>28</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>12</td>
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</table>

Table 15 Changes in ICP and peak ICP during each cooling episode in Patients 1-5

To examine the changes in ICP during cooling in more detail, each patient will be reported individually. ICP will be demonstrated graphically for each cooling period, along with T<sub>brain</sub>. Each studied episode will be represented by a black box, while those delivered but not studied by a blue box. A dashed black line represents 25mmHg.
Graphical representations of the temporal changes in ICP and $T_{brain}$ along with a description of ICP, sedation changes and use of barbiturates, for the entire study period, are presented in Appendix N.

**Patient 1**

![Graph showing changes in ICP and $T_{brain}$ during level 2 and 4 cooling in Patient 1](image)

Fig. 27 Changes in ICP and $T_{brain}$ during level 2 and 4 cooling in Patient 1

Patient 1 underwent two episodes of cooling early following injury. At the beginning of level 2 cooling ICP was 10mmHg. Following a small initial ICP rise there was a gradual increase in ICP peaking at 27mmHg, 12.25 hours from injury. The patient was noted to be biting on his endotracheal tube and as a result one of the sedating agents was increased. There was another rise in ICP to 33mmHg at 12.67 hours from injury and a further bolus of sedating agent was delivered at 12.75 hours from injury. Following this, ICP remained between 16 and 21mmHg. During level 4 cooling ICP fluctuated between 17 and 23mmHg. No further intervention was required and the increased sedative agent was gradually reduced to pre-cooling levels during this studied episode.
Fig. 28 Changes in ICP and $T_{\text{brain}}$ during level 2 and level 4 cooling in Patient 2

At the beginning of level 2 cooling ICP was 16mmHg. There was a steady rise in ICP during the early phase of level 2 cooling resulting in a peak of ICP (29mmHg) at 14 hours from injury (45 minutes of cooling). Boluses of a sedating agent were delivered at 13.9 and 14 hours from injury and an additional sedating agent was commenced at 14.5 hours from injury. Following this, ICP dropped to a minimum of 12mmHg but again increased to remain between 18 and 23mmHg for the remainder of the cooling episode. During level 4 cooling ICP remained between 12 and 24 mmHg, except for one spike to 31mmHg at 22.3 hours from injury (70 minutes of cooling). No intervention was required.
ICP was difficult to control throughout the entire study period. This is evidenced by an ICP of 31 mmHg at the onset of the first episode of level 3 cooling studied, despite surgery and an ongoing thiopentone infusion. A thiopentone infusion continued throughout the two studied periods, without additional sedating agents as the patient was fully burst suppressed on EEG. During this cooling period $T_{\text{brain}}$ fell steadily towards target temperature. ICP also trended downwards towards 25 mmHg, although there was a secondary rise towards the end of this period. At the completion of this first episode of level 3 cooling studied $T_{\text{brain}}$ was 37.2°C and ICP was 25 mmHg. During the second episode of level 3 cooling ICP was 25 mmHg at the onset and despite an early spike soon fell to be maintained between 18 and 22 mmHg. However as temperature continued to target temperatures towards the end of this cooling period, ICP rose and at the end of the cooling period was 31 mmHg. Thiopentone was also
stopped at 93 hours from injury, towards the end of this studied cooling episode. This patient died approximately 24 hours following this second phase of studied cooling.

Patient 4

Fig. 30 Changes in ICP and $T_{\text{brain}}$ during level 3 and 4 cooling in Patient 4

At 70 hours from injury thiopentone was commenced due to a sustained rise in ICP but stopped again at 82 hours form injury. Due to a sustained elevation in $T_{\text{brain}}$, level 3 cooling was commenced at 87.75 hours from injury and at this stage ICP was 25mmHg. The rise in ICP was sustained at this level and a thiopentone infusion was recommenced at 88 following injury. There were a number of spikes in ICP up to a maximum of 38mmHg despite maximal medical therapy and attempts to reduce temperature. As level 3 cooling failed to reduce temperature rapidly, level 4 cooling was commenced earlier than dictated by protocol, on the request of the treating clinicians. Although level 4 cooling did result in some reduction of $T_{\text{brain}}$, ICP continued to escalate and cooling was interrupted after only 70 minutes as the patient was transferred to theatre for emergency surgery.
Patient 5

Fig. 31 Changes in ICP and $T_{\text{brain}}$ during Level 2 and 4 cooling in Patient 5

ICP remained stable and within normal limits throughout the whole level 2 cooling process. During level 4 cooling ICP rose as $T_{\text{brain}}$ fell to target limits. Level 4 cooling was stopped following 135 minutes, as a result of a rise in ICP along with a fall in serum sodium and temperature reduction to within target limits. In order to counteract the rise in ICP additional boluses of sedative agents were administered at 88.9 and 89.3 hours from injury. Two boluses of thiopentone were then administered at 89.4 and 89.5 hours from injury. ICP settled following this.

Summary

Maintenance of ICP $<$25mmHg is the desired target on our ICU and in the event of a raised ICP in association with a raised $T_{\text{brain}}$, the reduction of $T_{\text{brain}}$ becomes even more significant. Looking closely at changes in ICP during the studied cooling episodes, it is clear that a trend in ICP reduction during studied cooling episodes is not evident.
Target temperature was not reached in any of the three studied level 2 cooling episodes and in two of these episodes ICP was higher at the end of cooling than at the beginning. During these two episodes (patient 1 and 2) additional sedation was required as a result of raised ICP. Peak ICP was also >25mmHg in each patient. ICP remained stable during the third studied level 2 cooling episode.

Level 3 cooling achieved target temperature in two out of three episodes. These two episodes were studied in the same patient (patient 3) and a thiopentone infusion was ongoing as a result of difficulties controlling ICP. During the first episode ICP was high but generally trended downwards. During the second episode ICP was relatively stable until towards the end when it began to rise. The third studied cooling episode (patient 4) was associated with an ICP that was increasingly difficult to control and a thiopentone infusion was recommenced. This episode was stopped early by the treating physicians due to a failure to reduce \( T_{\text{brain}} \) rapidly. Peak ICP was >25mmHg in all three studied level 3 cooling episodes.

In all four studied level 4 episodes ICP was higher at the end of cooling than the beginning and again peak ICP was >25mmHg in all episodes. This was despite level 4 reaching target temperature in three of the four studied episodes. The ICP rises in patient 4 and 5 were particularly surprising. ICP had been difficult to control before and during level 3 cooling in patient 4. However, ICP spiralled out of control during level 4 cooling and the patient was taken to theatre for an emergency decompressive craniectomy. The last recorded ICP before surgery was 45mmHg. Patient 5 had a stable ICP during level 3 cooling and the rise in ICP observed during level 4 cooling was unexpected. The clinical team looking after the patient commented that they believed the rise in ICP was a direct result of the cooling process.

Although the maintenance of normothermia was considered important by the clinical team it became even more vital in the presence of a raised ICP. However, observations from the studied cooling episodes suggest that in some situations not only is cooling not achieving a
reduction in $T_{\text{brain}}$ but also failing to reduce ICP. In fact, on occasion, rises in ICP were observed, contrary to the desired effect.

**BIS**

During studied cooling episodes BIS levels were recorded as a substitute for level of consciousness. The treating clinicians were blinded to BIS values. BIS was recorded due to the importance of adequate sedation in TBI patients, particularly in the event of a noxious stimulus, such as surface cooling. $T_{\text{brain}}$ and BIS values during studied cooling episodes will be demonstrated graphically for patients 1 to 5. Each studied episode will be represented by a black box, while those delivered but not studied by a blue box.

**Patient 1**

![Graph showing BIS and $T_{\text{brain}}$ changes](image)

Fig. 32 Changes in BIS analysis and $T_{\text{brain}}$ during level 2 and 4 cooling in Patient 1

In the fifteen minutes prior to onset of cooling BIS values were between 65 and 78.

Following the application of wet sheets, as part of level 2 cooling, the BIS value increased to 87. These values were not available to the medical staff however, on clinical examination
and review of physiological parameters, the patient was felt to be under sedated and as a result one of the sedating agents was increased at 10.3 hours from injury. The BIS value lowered following this until there was a further change of wet sheets at 11.75 hours from injury. At this stage the previously increased sedating agent had been lowered and the BIS values increased, to a maximum of 98. At 12.25 hours from injury the sedating agent was again increased as the patient was biting on the endo-tracheal tube following suctioning. A further bolus of sedating agent was delivered during level 2 cooling at 12.75 hours from injury. Following this, BIS values remained between 53 and 97.

During level 4 cooling BIS values remained at lower level between 33 and 59. Paralysing agents were added as per protocol for this cooling level. Clinically the sedating agents were decreased to pre-level 2 cooling rates and remained stable throughout the remainder of level 4 cooling. No additional boluses were required as a result of clinical review.

**Patient 2**

![Graph showing changes in BIS and T\textsubscript{brain} during level 2 and 4 cooling in Patient 2](image)

*Fig. 33 Changes in BIS analysis and T\textsubscript{brain} during level 2 and 4 cooling in Patient 2*
Prior to onset of level 2 cooling BIS values were between 50 and 60. Once level 2 cooling had begun the BIS values increased to the high 70’s. Additional boluses of sedating agent were administered at 13.9 and 14 hours from injury as ICP and MAP had increased. An additional sedating agent was added at 14.5 hours from injury due to ongoing raised MAP and ICP. Following the introduction of an additional sedating agent BIS fell dramatically and remained between 27 and 56 for the remainder of level 2 cooling.

During level 4 cooling the BIS values were more stable. Paralysis had been introduced as per protocol for this level of cooling. The sedating agents continued without change from level 2 cooling.

**Patient 3**

![Graph showing BIS and temperature changes](image)

Fig. 34 Changes in BIS analysis and $T_{\text{brain}}$ during two level 3 cooling episodes in Patient 3

Throughout the entire first level 3 cooling episode this patient received a paralysing agent and a thiopentone infusion for clinical reasons. These reasons included an ICP that was difficult to manage, despite an emergency decompressive craniectomy. BIS values remained between 0 and 10 this first studied cooling episode.
During the second level 3 cooling BIS values began at higher levels (57-66). At the beginning of this episode the patient had a new ICP/temperature probe inserted at the bedside. BIS fell to 0, 65 minutes from the onset of cooling. During this cooling episode BIS was 0 for approximately 70% of the time. There were some fluctuations between 1 and 5 at the end of the cooling period. Thiopentone had been switched off 30 minutes prior to these small fluctuations.

**Patient 4**

![Graph showing BIS and Temperature (°C) from 85 to 95 hours from injury. Level 3 and Level 4 cooling are indicated. BIS values range from 0 to 100, and Temperature from 33°C to 39°C.](image)

Fig.35 Changes in BIS analysis and $T_{\text{brain}}$ during level 3 and 4 cooling in Patient 4

Level 3 cooling was commenced at 87.75 hours from injury and a thiopentone infusion was recommenced at 88 hours from injury. The infusion had previously been stopped at 82 hours from injury. BIS was highest at the beginning of level 3 cooling (maximum of 23). Throughout the remainder of level 3 and level 4 cooling BIS remained low (<20).
Fig. 36 Changes in BIS analysis and $T_{\text{brain}}$ during level 2 and 4 cooling in Patient 5

At the onset of level 2 cooling BIS was 57 and remained between 30 and 60 for the remainder of this episode. The infusion of sedating agents remained stable throughout. During level 4 cooling BIS also remained between 30 and 60. Two boluses of sedating agent and two boluses of thiopentone were administered between 88.9 and 89.5 hours from injury due to an unexpected rise in ICP.

**Summary**

The use of BIS in the ICU setting, particularly in brain injured patients, remains controversial. However, during studied cooling episodes changes in the BIS trends were observed to be correlated with clinical findings. During the course of these studied episodes the clinical team was blinded to the BIS figures. In patient 1 sedating agents were increased on three occasions during level 2 cooling and corresponded to periods when BIS was $>80$. There were periods during this studied episode when BIS was $>80$ and sedation was not increased by the medical staff. During another studied level 2 cooling (patient 2), additional
sedation was again felt necessary by the medical staff at a time when BIS levels had risen to the high 70’s. A barbiturate coma was induced in both patient 3 and 4 and BIS levels correlated with this. Severe brain injury may have also contributed to the very low BIS values, particularly in patient 3. During the second studied cooling episode of level 3 in patient 3, BIS values were 0 for 70% of the episode. BIS values for Patient 5 remained stable throughout the cooling process. Additional sedation was added at the end of level 4 cooling for a rise in ICP, not as a result of clinical findings of under sedation.

Absolute BIS values may not be as important as the trends observed, and in two patients during level 2 cooling there was an observed rise in BIS that correlated with clinical findings of under sedation. In two patients low BIS values were also observed, in keeping with a severe brain injury (both patients required an emergency decompressive craniectomy) or barbiturate coma. The final patient studied had stable BIS values and stable sedation requirements.

**CPP**

Table 16 demonstrates the CPP at the beginning and end of every cooling episode studied and the differences between them. It also demonstrates the percentage of time CPP was <60mmHg during each studied cooling phase.

To examine the changes in CPP during cooling in more detail, each patient will be reported individually. CPP will be demonstrated graphically for each cooling period, along with noradrenaline requirements. Each studied episode will be represented by a black box, while those delivered but not studied by a blue box. A dashed black line represents 60mmHg. Graphical representations of the temporal changes of CPP and $T_{\text{brain}}$ and noradrenaline requirements, for the entire study period, are presented in Appendix O. A description of CPP, sedation changes and noradrenaline use are also in Appendix O.
<table>
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<th>Patient Number</th>
<th>Level of Cooling</th>
<th>CPP&lt;sub&gt;start&lt;/sub&gt; (mmHg)</th>
<th>CPP&lt;sub&gt;end&lt;/sub&gt; (mmHg)</th>
<th>CPP&lt;sub&gt;start&lt;/sub&gt;-CPP&lt;sub&gt;end&lt;/sub&gt; (mmHg)</th>
<th>% time CPP &lt;60mmHg</th>
<th>Lowest CPP (mmHg)</th>
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Table 16 Changes in CPP during studied cooling episodes in Patients 1-5

Patient 1

Fig. 37 Changes in CPP and noradrenaline requirements during cooling in Patient 1
Following an initial rise in CPP beyond 60mmHg, CPP fell suddenly to below the target value at approximately 10.8 hours from injury. This occurred following an increase in one of the sedating agents by a member of the clinical team, as the patient was felt not to be adequately sedated for level 2 cooling. Noradrenaline was commenced 12.5 hours from injury and CPP rose to >60mmHg. The noradrenaline infusion was continued throughout the remainder of level 2 cooling and CPP remained above target values. During level 4 cooling the noradrenaline infusion was decreased and stopped at 18.6 hours from injury. CPP remained stable and well maintained throughout this level 4 cooling.

---

**Patient 2**

![Graph](image)

Fig. 38 Changes in CPP and noradrenaline requirements during cooling in Patient 2

CPP was abnormally high, at a level of >90mmHg, for 90% of level 2 cooling. No vasopressors were delivered. There was a sudden drop in CPP at 17.5 hours from injury, as a result of a drop in MAP rather than a change in ICP. Boluses and an infusion of an additional sedating agent had been administered approximately 3 hours prior to this but there were no
changes in sedation or other medications during the period of the CPP drop. No other changes in physiological parameters were noted. CPP remained at a more appropriate level (60 to 69 mmHg) throughout the final stages of level 2 cooling. No vasopressors were required during level 4 cooling. Apart from one transient fall in CPP to 53 mmHg, CPP remained >60 mmHg, reaching a maximum level of 79 mmHg.

Patient 3

![Graph showing changes in CPP and noradrenaline requirements during cooling in Patient 3](image)

Fig. 39 Changes in CPP and noradrenaline requirements during cooling in Patient 3

Although CPP was generally < 60 mmHg (52-61 mmHg) during the first studied level 3 cooling episode, significant doses of noradrenaline were required to maintain CPP at this level. During the second studied level 3 cooling episode, the patient had deteriorated and CPP was maintained at levels much below the target levels (36-54 mmHg). This was despite a dramatic increase in the noradrenaline dosage the patient was receiving. Towards the end of the second cooling episode the noradrenaline infusion was reduced by the clinical team. This resulted in a drop in CPP but was felt to be necessary to counteract the profound
peripheral vasoconstriction the patient was experiencing. A dobutamine infusion was added 93 hours from injury.

**Patient 4**

![Graph showing CPP and noradrenaline requirements during cooling in Patient 4]

- **CPP**: Well maintained above 60mmHg for approximately 80% of the level 3 cooling episode. Transient falls in CPP corresponded to peaks in ICP, particularly at approximately 89 hours from injury. Noradrenaline requirements were stable. During level 4 cooling CPP fell as ICP spiralled despite maximal medical therapy. Noradrenaline was reduced slightly due to profound peripheral vasoconstriction. The patient was transferred to theatre for an emergency decompressive craniectomy.

**Fig. 40 Changes in CPP and noradrenaline requirements during cooling in Patient 4**
Fig. 41 Changes in CPP and noradrenaline requirements during cooling in Patient 5

During level 2 cooling CPP was maintained at >59mmHg with a relatively stable noradrenaline infusion. At times CPP was greatly above the recommended target reaching a maximum of 91mmHg. CPP was also maintained at a level >60mmHg with a relatively stable noradrenaline infusion during level 4 cooling. At the beginning of this cooling episode CPP reached a maximum of 93mmHg. CPP did not fall, despite the rise in ICP, towards the end of this studied episode.

Summary

During the first studied level 2 cooling episode noradrenaline was commenced 135 minutes into cooling. This resulted from an increase in ICP, thought to be secondary to inadequate sedation for the cooling manipulations. The level 2 cooling episode studied in patient 2
demonstrated a rise in CPP without noradrenaline requirements. CPP had been in the low 90’s prior to the onset of cooling but rose to a maximum of 112mmHg. ICP had also risen and additional sedating agents were required to lower ICP and the markedly raised MAP. During the final studied level 2 episode, CPP was maintained >60mmHg for the most part with a relatively stable noradrenaline infusion, continued from prior to cooling onset. At times however, CPP was much higher than target values.

Two level 3 cooling episodes were studied in patient 3. Noradrenaline infusions were continued from prior to cooling onset on both occasions. Despite this CPP remained between 52 and 61mmHg on the first occasion and 36 and 54mmHg on the later second occasion. Towards the end of the second episode of level 3 cooling the noradrenaline infusion was reduced and a dobutamine infusion commenced. During the final studied level 3 cooling episode, noradrenaline was again continued from prior to onset of cooling. CPP was generally >60mmHg with transient drops that corresponded to ICP peaks and no changes to the noradrenaline infusion resulted.

Four level 4 cooling episodes were studied. In patient 1, CPP was high at the outset (85mmHg) and the noradrenaline infusion commenced during level 2 cooling was reduced and stopped. Despite this CPP remained between 77 and 85mmHg during the remainder of the cooling episode. Generally CPP remained >60mmHg and <80mmHg during level 4 cooling without vasopressors support in patient 2. CPP was also raised (93mmHg) at the onset of level 4 cooling in patient 5, with a continued noradrenaline infusion. The infusion was decreased slightly throughout the cooling episode. CPP did not fall despite a rise in ICP.

In summary, during studied cooling episodes it was observed that generally noradrenaline was either continued from before cooling or started during cooling to maintain CPP or CPP was higher than recommended targets.
3.2.7 The Effect of Cooling on Biochemical Markers of Injury and Inflammation

**S100b**

S100b was measured during the study phase and studied cooling episodes. The table below demonstrates initial and peak S100b levels along with timing of sample. GOS has also been included for each patient.

<table>
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<th>Initial S100b (µg/l)</th>
<th>Time of Sample (Hours from Injury)</th>
<th>Peak S100b (µg/l)</th>
<th>Time of Sample (Hours from Injury)</th>
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</table>

Table 17 Initial and peak S100b levels and sample timing for each study patient

To examine the changes in S100b in more detail, each patient will be reported individually. S100b will be demonstrated graphically for each study period, along with $T_{\text{brain}}$. Each studied cooling episode will be represented by a black box, while those cooling episodes delivered but not studied by a blue box. Each level will be labelled. Due to sample timing, S100b will be demonstrated throughout the whole study period only for each patient.
**Patient 1**

Fig. 42 Changes in S100b and $T_{\text{brain}}$ throughout the study period in Patient 1

S100b was high (1.79$\mu$g/l$^{-1}$) on admission to ICU, 6.5 hours following injury. The next two samples were taken at 10 and 10.75 hours, 15 minutes prior to and 30 minutes after the start of a studied level 2 cooling episode. The values were equal and slightly higher than admission levels. The next level taken 180 minutes (13.25 hours from injury) from the onset of level 2 cooling, showed a convincing rise in S100b levels to 3.32$\mu$g/l$^{-1}$. S100b was again sampled at the end of level 2 cooling and although the value had fallen, it remained greater than 2$\mu$g/l$^{-1}$ and admission levels. Sampling at 30 minutes from the onset of level 4 cooling demonstrated a further slight fall. A further rise was however demonstrated 180 and 300 minutes from the onset of level 4 cooling, rising to 2.29 and 2.25 respectively. Throughout the remainder of the study period S100b gradually declined.
Fig. 43 Changes in S100b and $T_{\text{brain}}$ throughout the study period in Patient 2

Admission S100b, taken at 13 hours from injury and 15 minutes before the onset of level 2 cooling, was 0.51µg{l}^{-1}. There was a very slight rise during level 2 cooling to a maximum of 0.58µg{l}^{-1}, which then fell, at the end of the cooling episode, to equal the admission value.

During level 4 cooling there was a further rise from 0.47µg{l}^{-1} (30 minutes from onset) to 0.72µg{l}^{-1} (180 minutes from onset). Throughout the remainder of the study period there was a gradual fall in S100b.
The initial value of S100b, 5 hours from injury, was 1.99 µg/l. Although there was an initial decline in the S100b values, they began to rise again with the sample taken at 30.33 hours from injury. S100b rose to a maximum of 1.98 µg/l at 44.5 hours from injury. This rise corresponded with a period when ICP became more difficult to control and T\(_{\text{brain}}\) was falling, resulting in an emergency decompressive craniectomy 52 hours from injury. Following this, S100b continued to fall until the end of the study period when there was another rise in S100b to 1.72 µg/l. This final measurement corresponded with marked clinical deterioration and was sampled approximately five hours before the patient died. No rise in S100b was demonstrated during the two studied cooling episodes.
The initial value of S100b, 14 hours following injury was 4.17 \mu g l^{-1}. This rose slightly at 16.4 hours from injury to 4.47 \mu g l^{-1}. This corresponded with an episode of mildly elevated T_{brain} for which no cooling was required as it settled rapidly. The first sample to fall below 2 \mu g l^{-1} was at 54 hours from injury. Following this S100b fell, until there was a very slight rise/flattening of the decline, at 30 minutes into a studied level 3 cooling episode (0.89 \mu g l^{-1}) when compared to the sample taken 15 minutes before the onset of cooling (0.86 \mu g l^{-1}).

S100b fell throughout the remainder of the study period until there was another small rise 120.6 hours from injury. This small rise of 0.08 \mu g l^{-1} corresponded with a raised T_{rectal}. There were no detected changes in S100b in the peri-operative period.
The first measurement of S100b at 13.6 hours from injury was 0.38µgl⁻¹. There was a very small rise (0.07µgl⁻¹) in S100b at 35 hours from injury. This did not correspond with a raised ICP or T\textsubscript{brain}. There was a second very small rise that corresponded to an elevated T\textsubscript{brain} that was not studied. During the studied level 2 cooling episode S100b remained static (0.16µgl⁻¹) at 30, 180 and 300 minutes from onset. There was a slight fall during level 4 cooling. There was another small rise from 0.11µgl⁻¹ at 95 hours from injury to 0.17µgl⁻¹ at 131 hours from injury. This rise corresponded with a rise in T\textsubscript{brain} and a level 2 cooling episode, started at 124 hours from injury, which was not studied.
Fig. 47 Changes in S100b and T_{brain} throughout the study period in Patient 6

On admission to ICU, 13 hours following injury, S100b was 0.53 µg/l. There was a rise in S100b to above admission levels (0.79 µg/l) at 37 hours following injury. This did not correspond with any difficulty controlling ICP or maintaining CPP or with a raised T_{brain} or cooling episode. Sedation had been switched off at 32 hours and noradrenaline stopped at 36 hours from injury. During the remainder of the study period S100b continued to fall.
Fig. 48 Changes in S100b and $T_{\text{brain}}$ throughout the study period in Patient 7

The first sample was measured 16 hours from injury and was 0.24 $\mu$g l$^{-1}$. During the remainder of the study period S100b generally fell. However the sample at 64 hours from injury demonstrated a small rise (0.05 $\mu$g l$^{-1}$). This corresponded with a period of raised $T_{\text{brain}}$. No cooling episode was delivered as sedation was switched off.
The first sampled S100b was at 22.5 hours from injury and was 0.71µg/l. There was no fall between the samples at 35 hours and 46.5 hours from injury (0.42µg/l). Prior to 35 hours, T_{brain} had been spontaneously low and ICP had been difficult to control. Thiopentone was stopped at 39.5 hours while an additional sedating agent was also stopped 36 hours from injury. There was a small rise of 0.07µg/l in S100b at 70.5 hours from injury when compared to the previous sample at 59 hours from injury. Following this S100b continued to fall.
Summary

The pattern of clearance of S100b was different for each patient when temporal changes were observed. Patient 1 demonstrated a rise from baseline (1.87 to 3.32μg/l-1) at 13.25 hours from injury. This rise occurred 3 hours into a studied level 2 cooling episode. From this point the S100b levels dropped on the following two samples only to rise again (1.98 to 2.29μg/l-1) at 19.5 hours from injury. This second rise occurred 3 hours into a studied episode of level 4 cooling. Following this second rise the S100b serum levels gradually fell throughout the remaining sampling time. A small rise in serum S100b (0.47 to 0.72μg/l-1) was also observed in patient 2 during an episode of studied level 4 cooling, 20 hours from injury. S100b levels fell throughout the remainder of the sampling time. A rise in S100b, not associated with cooling, was also demonstrated in patient 3. Levels increased from 1.63μg/l-1 at 28 hours from injury to 1.98μg/l-1 at 44.5 hours from injury. This corresponded with a period of increasing instability, with rising ICP and falling T_brain, despite maximal medical therapy. The sample at 44.5 hours was taken only 5.5 hours before patient 3 underwent a decompressive craniectomy. Interestingly, S100b levels were lower on return from theatre (1.05μg/l-1) and continued to fall, even during studied cooling episodes, until the sample rose again at 116 hours from injury (1.72μg/l-1). This sample was taken during a period of clinical deterioration and only 1 hour before the patient died. Patient 4, whom had the highest initial serum S100b value, did have a rise at the beginning of the study period from 4.17μg/l-1 at 16 hours from injury to 4.47μg/l-1 at 16.5 hours from injury. This corresponded with a period of slightly raised temperature that settled rapidly without intervention and also a raised ICP that also settled following increased sedation and the commencement of a thiopentone infusion. During the remainder of the sampling serum S100b levels gradually declined. There was no rise in S100b demonstrated prior to a decompressive craniectomy performed at 93 hours from injury. A small rise in serum S100b levels was also observed in patient 6 at 37 hours from
injury. This did not correspond with a raised $T_{\text{brain}}$, cooling episode or difficulties managing ICP or CPP. It did occur shortly after the patient had sedation and noradrenaline switched off. Patient 5 and 7 had serum S100b levels that were persistently below 0.5µg/l. Patient 8 had an initial level of 0.71µg/l but this rapidly fell to <0.5µg/l and remained below this value. No secondary rises were demonstrated in any of these three patients.

In association with cooling, a large rise in serum S100b was observed in patient 1 during a studied level 2 cooling episode and a smaller rise during level 4 cooling. A small but definite rise during a level 4 studied episode was also observed in patient 2. During level 2 cooling in patient 4 S100b remained the same in the three serum samples taken in the course of the studied episode.

**Inflammatory Markers**

IL-6 and TNF-α were measured during the study phase and studied cooling episodes. Due to sample timing, both cytokines will be demonstrated throughout the whole study period for each patient, along with $T_{\text{brain}}$. Each studied cooling episode will be represented by a black box, while those cooling episodes delivered but not studied by a blue box. Each level will be labelled.
Patient 1

Fig. 50 Changes in TNF-α, IL-6 and T_{brain} throughout the study period in Patient 1

IL-6 was 97pgml\(^{-1}\) on admission. It then rose to 225pgml\(^{-1}\) three hours later, just prior to the start of a cooling episode. During level 2 cooling, IL-6 peaked at the end of the episode reaching 276pgml\(^{-1}\), while during level 4 cooling IL-6 reached a peak of 339pgml\(^{-1}\), three hours into the episode. Following this IL-6 reached a peak at 42 hours from injury. In order to maintain CPP noradrenaline had been recommenced at 37 hours and ICP had become more difficult to control from 40 hours from injury. IL-6 levels fell during the remainder of the study.

TNF-α levels remained 0.59pgml\(^{-1}\) during level 2 cooling. After a small fall levels rose to 0.82pgml\(^{-1}\) 180 minutes into level 4 cooling. Throughout the remainder of the study period TNF-α gradually increased to reach a maximum 2.36 pgml\(^{-1}\) 102 hours from injury.
Fig. 51 Changes in TNF-α, IL-6 and $T_{\text{brain}}$ throughout the study period in Patient 2

IL-6 levels were 64.9 pgml$^{-1}$ on admission. The level fell at the beginning of level 2 cooling following by a rise to a maximum of 272 pgml$^{-1}$ at the end of this cooling episode. Levels fell during level 4 cooling. Following this, levels remained below the peak observed at the end of level 2 cooling, until 77.5 hours from injury when levels surged to 1580 pgml$^{-1}$. This corresponded with a period of low CPP which resulted in the need for a noradrenaline infusion. Six hours prior to this sample thiopentone had been commenced as a result of increasing ICP. Along with this, oxygen requirements were increasing as a result of a proven chest infection. IL-6 remained high until the sample at 101.5 hours from injury. During the remainder of the study there was a rise in levels, as noradrenaline requirements increased, ICP became more difficult to control and $T_{\text{brain}}$ spontaneously fell.

TNF-α was 0.46 pgml$^{-1}$ on admission but rose massively to 7.68 pgml$^{-1}$, 30 minutes into level 2 cooling. Following this, levels fell to 0.64 pgml$^{-1}$ at 41.5 hours from injury and then gradually rose throughout the remainder of the study period.
Fig. 52 Changes in TNF-α, IL-6 and T$_{\text{brain}}$ throughout the study period in Patient 3

The first sample of IL-6, taken at 19 hours from injury, was 295pg/ml$^{-1}$. Values then fell over the course of 37 hours to reach 91.5pg/ml$^{-1}$. IL-6 then increased in conjunction with a raised T$_{\text{brain}}$ and a delivered and studied level 3 cooling episode. It reached a high of 188pg/ml-1, three hours into this episode. IL-6 peaked again during the second delivered and studied cooling episode, reaching 405pg/ml$^{-1}$. This peak also occurred three hours following the onset of cooling. Another IL-6 peak occurred 104 hours from injury, reaching 1056pg/ml$^{-1}$. At this stage ICP was rising and CPP was falling, resulting in the need to increase noradrenaline requirements and to recommence a thiopentone infusion.

There was a gradual increase in TNF-α from the first sample (0.21pg/ml$^{-1}$) until 88.25 hours from injury, when it reached 1.54pg/ml$^{-1}$. This period included a delivered and studied level 3 cooling episode. During the next studied cooling episode and in a sample taken 102.5 hours from injury TNF-α values gradually fell to 0.31pg/ml$^{-1}$. In the sample taken 104 hours from injury TNF-α had risen sharply to 1.33pg/ml$^{-1}$, in conjunction with a rise in ICP and fall in CPP.
When first sampled at 14 hours from injury, IL-6 was 249pgml$^{-1}$. Following a rise to 293pgml$^{-1}$, 2.5 hours later, IL-6 fell to reach a low of 44pgml$^{-1}$, 54 hours from injury. Until the end of the two studied cooling episodes, just prior to an emergency decompression, IL-6 remained between 50 and 75pgml$^{-1}$. Post surgery IL-6 rose to reach a peak of 303pgml$^{-1}$, 108 hours from injury. There was a rise in TNF-α to 2.39pgml$^{-1}$, 30 hours from injury. Following this, TNF-α fell and then rose again to 2.26pgml$^{-1}$, 78 hours from injury. During the two studied cooling episodes TNF-α remained between 1.9 and 2.1pgml$^{-1}$. Post emergency decompressive craniectomy, TNF-α was sampled at 103 hours from injury and was 1.71pgml$^{-1}$. 

Fig. 53 Changes in TNF-α, IL-6 and $T_{\text{brain}}$ throughout the study period in Patient 4
Fig. 54 Changes in TNF-α, IL-6 and $T_{\text{brain}}$ throughout the study period in Patient 5

Although there were some fluctuations, IL-6 generally rose from admission values to reach a peak of $491\text{pgm}l^{-1}$. This coincided with a rise in $T_{\text{brain}}$ and occurred 30 minutes into a studied episode of level 2 cooling. During the remainder of level 2 cooling and level 4 cooling IL-6 remained between $240$ and $280\text{pgm}l^{-1}$. Five hours post cooling there was a smaller peak to $344\text{pgm}l^{-1}$. A much larger peak to $887\text{pgm}l^{-1}$ occurred at 131 hours from injury. This coincided with a raised $T_{\text{brain}}$ and a delivered episode of level 2 cooling that breached protocol as the patient was not sedated.

Throughout most of the studied period, including the two studied cooling episodes, TNF-α remained between 1 and $2\text{pgm}l^{-1}$. At 119 hours from injury, the sampled serum demonstrated a rise above $2\text{pgm}l^{-1}$ and reached a peak in the next sample to $5.45\text{pgm}l^{-1}$, 131 hours from injury. The final sample remained high at $4.46\text{pgm}l^{-1}$, 143 hours from injury. These final three samples coincided with a period of raised $T_{\text{brain}}$ while the peak sample also coincided with a level 2 cooling episode delivered without sedation.
Patient 6

IL-6 rose from admission to reach 321pgml$^{-1}$, 25.5 hours from injury. Throughout the remainder of the study period IL-6 gradually fell.

TNF-α had a reasonably stable course throughout the study period, remaining between 0.5 and 0.9pgml$^{-1}$.
Fig. 56 Changes in TNF-α, IL-6 and T_{brain} throughout the study period in Patient 7

Due to a laboratory error only IL-6 results were made available for this patient.

IL-6 rose to reach a peak of 300pgml^{-1} 52.5 hours from injury. A second smaller peak occurred at 88.3 hours from injury. The T_{brain} probe was removed 86 hours from injury. The last recorded temperature was 39°C.
Fig. 57 Changes in TNF-α, IL-6 and $T_{\text{brain}}$ throughout the study period in Patient 8

Due to a laboratory error only IL-6 results are available for this patient.

From the first sample to 60 hours from injury IL-6 remained between 70 and 105pgml$^{-1}$. IL-6 then rose to reach a peak of 241pgml$^{-1}$, 83.25 hours from injury. The next sample was obtained during a delivered but not studied cooling episode and was 219pgml$^{-1}$. The final sample was taken just before a delivered but not studied level 2 cooling episode.
Fig. 58 Summary of changes in IL-6 in all eight patients studied throughout the study period.

Fig. 59 Summary of changes in TNF-α throughout the study period in Patient 1 to 6.
The course of both IL-6 and TNF-α, during the study period, was different for each patient. Broadly speaking, over the course of the study period, TNF-α had a tendency to slowly rise. IL-6 had a much more fluctuant pattern but there seemed to be a loose tendency to decrease during the study period. IL-6 also appeared to have more deviations from baseline values that coincided with significant patient events. Patient 2 and 3 had large rises in IL-6 at times when CPP and ICP were difficult to maintain. Patient 1 had a small rise in IL-6 also at a time of difficult ICP and CPP control. Patient 5 had a large rise in IL-6 and TNF-α which coincided with a level 2 cooling episode delivered without sedation.

During studied cooling episodes some fluctuations were also observed, particularly in IL-6. In the three studied level 2 cooling episodes IL-6 rose. Two out of the three level 3 and one out of the four level 4 cooling episodes, also demonstrated a rise in IL-6 at some point during cooling. The rises observed varied in amplitude.

A large rise in TNF-α was also demonstrated at the beginning of level 2 cooling in patient 2.
Chapter 4

Discussion
In this chapter the results of the two linked studies are discussed in more detail. The controversies surrounding temperature management following TBI will be further explored and the possibilities for the future discussed.

4.1 Clinical

4.1.1. The burden of TBI

In a one year period 72 patients were admitted to SRFT ICU from the Greater Manchester area. From the 57 case notes reviewed patients tended to be young and male. As evidenced by their need to be admitted to ICU, these patients had suffered a serious, severe or critical TBI. This is also evidenced by their low GCS and high AIS scores. About a quarter of patients reviewed did not survive. The majority (68%) of the patients who did survive had a good outcome (GOS 4 and 5) and the remainder (7%) had a poor outcome (GOS 2 and 3). These findings were reflected in the small number of patients recruited to the observational study.

These figures are only the tip of the iceberg, as they do not include patients admitted to neurosurgical HDU, general neurosurgical wards or those who have attended A&E and either been admitted under the care of A&E or discharged home. Considering patients with a severe TBI only, it is clear that such large numbers have a profound effect on service requirements, not just for neurosurgery and ICU. The nature of the sequelae following severe TBI means that a multidisciplinary approach is required and therefore many teams are involved in all stages of TBI management.

The consequences of severe TBI to families and communities should also be considered. In the early stages families face an uncertain future with the possibility of their loved one not surviving or surviving with disability. In the longer term families may have to endure
ongoing rehabilitation and provide for and support a previously independent relative. This has obvious practical, emotional and financial implications. Severe TBI also impacts on the community due to the potential loss of an active, working member of the community who requires support.

The impact of severe TBI on the patient and their family, the health service and the local and national community cannot be over emphasised. Appropriately TBI has been described as a ‘silent epidemic’.
4.2 Temperature Following Traumatic Brain Injury

4.2.1 Temperature

The work of Wunderlich on temperature appears outdated, yet his concept of ‘normal’ and ‘fever’ thresholds continue to be used by many in routine clinical practice. There is an increasing body of evidence that the conventional thresholds of ‘normal’ and ‘fever’ should be abandoned and that temperature readings should be considered on an individual basis taking into consideration gender, age and time of day (Mackowiak, Wasserman, and Levine 1992; Sund-Levander, Forsberg, and Wahren 2002).

4.2.2 Temperature Measurement

In the UK and Ireland all neurosurgical ICU’s measure temperature in patients following a severe TBI (Johnston et al. 2006). It is considered an important and routine component of patient monitoring. Despite this the majority of units use methods of temperature measurement which are considered poor substitutes for core temperature and are therefore inadequate substitutes of $T_{\text{brain}}$. At the time of this ICU questionnaire, skin fold temperature was used in 42% of centres. Peripheral temperature and therefore skin fold temperature is dependent on many factors and measurements are widely variable even within the same patient (Frim et al. 1990; Zhu and Xin 1999). Tympanic temperature measurements are also used in a significant proportion of units. These measurements have been shown to be influenced by many factors and also to be a poor substitute of core temperature (Doezema, Lunt, and Tandberg 1995; Amoateng-Adjepong, Del Mundo, and Manthous 1999; Nierman 1991; Moran et al. 2007).

Other methods of temperature measurement such as rectal, bladder, oesophageal and nasopharyngeal, are often assumed to reflect core temperature and therefore $T_{\text{brain}}$ more
closely. However, studies have demonstrated that these measurements do not always accurately reflect $T_{\text{brain}}$, particularly at times of temperature flux (Childs et al. 2005; Henker, Brown, and Marion 1998; Rumana et al. 1998a; Stone et al. 1995).

The local protocol for TBI management on ICU directs the use of $T_{\text{rectal}}$ if $T_{\text{brain}}$ is not available. Despite this, the patient review clearly demonstrated that tympanic temperature measurements were being monitored rather than $T_{\text{rectal}}$ or $T_{\text{brain}}$ in a large proportion of patients.

It is often assumed that temperature recordings from ‘core’ sites can be used as surrogates for $T_{\text{brain}}$, despite increasing evidence to the contrary. Concerns that the insertion of $T_{\text{brain}}$ probes may result in further injury are often cited for their lack of use. Most TBI patients admitted to ICU in the UK and Ireland have ICP monitoring, and combined ICP/temperature probes are available. In addition direct $T_{\text{brain}}$ measurement has been shown to be safe in these patients (Rumana et al. 1998b). However, direct measurement of $T_{\text{brain}}$ does come with its own controversies. Animal and human studies have demonstrated a temperature gradient between the surface and core of mammalian brains (Mellergård 1994; Mellergård 1995; Zhu et al. 2006). In humans, the core $T_{\text{brain}}$ has been measured to be on average 0.5ºC higher than the epidural temperature (Mellergård 1994; Mellergård 1995). At present there is no consensus about temperature probe brand or site of placement, as intra-ventricular, intraparenchymal and subdural temperature probes are all currently available. Currently no evidence is available as to whether areas of injured brain, such as contusion, should be avoided when inserting the probe.

In summary, temperature measurement is routinely measured following severe TBI, but the conventional thresholds used by many in daily clinical practice would seem to be outdated. Direct $T_{\text{brain}}$ measurement would appear to be the most logical way to monitor temperature in TBI patients admitted to Neurosurgical ICU, despite the controversies around its use.
Temperature flux is a common occurrence in TBI patients and it is during these times that accurate temperature measurement is crucial, particularly if intervention is to be undertaken appropriately. If $T_{\text{brain}}$ cannot be directly measured, then any substitute measurement should adequately represent core temperature and clinicians should be aware of the inherent problems in different methods of measurement.

4.2.3 Fever versus Hyperthemia

Numerous studies have demonstrated a high frequency of raised temperature in ICU following severe TBI, particularly within the first 72 hours of admission (Albrecht, Wass, and Lanier 1998; Jones et al. 1994; Kilpatrick et al. 2000; Rossi et al. 2001; Stocchetti et al. 2002; Sacho and Childs 2008). The true nature of a raised temperature, particularly in the early stages, following severe TBI remains unclear and the fever versus hyperthermia debate continues. It seems likely that most raised temperature episodes in the early stages are fevers, with a new thermal set point, as a result of the numerous cellular and molecular cascades set into motion by the injury as part of the acute phase response. If this is the case, a new thermal set-point may contribute towards some of the failures experienced during attempts to reduce a raised temperature. It is however noteworthy that anti-pyretics, which are thought to reduce an elevated thermal set-point, are generally ineffective (Albrecht, Wass, and Lanier 1998; Mayer et al. 2001; Poblete et al. 1997). In most cases of early raised temperature underlying infection seems unlikely, as most infectious ‘fevers’ develop, on average, 4 days after admission (Rabinstein and Sandhu 2007). The possibility of damage to the central thermoregulatory centre and pathways must also be considered.

In animal models there is some evidence to suggest that fever is a beneficial host response to infection (Kluger et al. 1996; Villar et al. 1994). In humans, fever has been reported as part of a normal adaptive response and to be beneficial in certain circumstances, such as sepsis.
(Barone 2009; Bryant et al. 1971; Mackowiak, Wasserman, and Levine 1992; Weinstein et al. 1978). Indeed, some studies have demonstrated that treating fever with anti-pyretics may be harmful (Doran et al. 1989; Graham et al. 1990; Schulman et al. 2005; Mackowiak, Wasserman, and Levine 1992). In a randomised prospective study of 82 trauma patients without TBI, admitted to ICU, mortality was significantly higher in the group of patients receiving aggressive therapy for a raised temperature (>38.5°C) when compared to a permissive treatment group (temperatures allowed to rise to 40°C) (Schulman et al. 2005). If the temperature seen frequently in the early stages of TBI is assumed to be a ‘fever’, it is possible that interventions to reduce temperature may interrupt a normal adaptive response.

### 4.2.4 Raised Temperature following Traumatic Brain Injury

Many clinicians regard a raised temperature following TBI to be potentially harmful as evidenced by the maintenance of normothermia by the majority (88%) of ICU’s in the UK and Ireland. However, in experimental animal models of TBI and raised temperature, the evidence is conflicting. One study demonstrated an increase in the degree of structural damage and mortality in rats exposed to a raised temperature when compared to rats maintained at normothermia following TBI (Dietrich et al. 1996). By contrast, in another study no change in outcome in rats exposed to a raised temperature when compared to those maintained at normothermia was found. Most experimental animal (rodent) studies have examined the effects of raised temperature in a post-ischaemic setting. This work has demonstrated not only increased mortality and worsened outcome but also acceleration of ischaemic injury and increased severity of histopathological damage (Busto et al. 1987; Dietrich et al. 1991; Dietrich, Busto, Halley, et al. 1990; Dietrich, Busto, Valdes, et al. 1990; Kim et al. 1996). These studies are often quoted in reference to raised temperature following TBI, despite the fact that this data relates to ischaemic injury.
There are considerable challenges when translating results from rodent models to patients in TBI. Firstly, the different dimensions and surface area of human and rodent brains, and their different body to surface ratios, mean that rodents are more strongly influenced by environmental temperature. Rodents also have a higher CBF and differences in vascular anatomy that could result in differing temperature gradients (Zhu et al. 2006). The methods of TBI induction varies between studies and contusional volume after experimental TBI can vary greatly (2.14mm$^3$ to 65mm$^3$) depending on the model used (Robertson et al. 2000). Other confounding problems include differing methods of temperature measurement and timing of events. One major problem with rodent studies stems from the methods used to raise temperature, as they usually involve induction of hyperthermia rather than fever. This brings us back to the fundamental fever versus hyperthermia debate following TBI. If we believe that the raised temperature in the initial phase of TBI is truly fever, can we legitimately extrapolate these findings from animals to patients?

Patient studies of raised temperature following TBI are no less open to scrutiny. Several studies have suggested that increased temperature following TBI is related to an increased length of hospital stay and worsened outcome in both adults and children (Diringer et al. 2004; Suz et al. 2006; Natale et al. 2000). Diringer et al. did note that in this adult population, the impact on mortality and hospital stay was dependant on the degree of temperature rise, with temperature rises to >39°C having a greater impact than 37.4-38.4°C. None of these groups used $T_{\text{brain}}$ measurements but instead a combination of rectal, axillary and oral measurements, all of which have been shown to be poor substitutes for $T_{\text{brain}}$. The definition of a raised temperature was different in each study as were the resultant interventions. The population of patients in the study by Diringer et al. was made up of critically ill neurosurgical and neurology patients. In 2002, Stocchetti et al. demonstrated that patients with a raised temperature had an increased ICU stay but there was no relationship.
between presence or duration of a raised temperature and 6-month outcome (GOS) (Stocchetti et al. 2002). Temperature measurements were either core (bladder, rectal or pulmonary artery) and/or peripheral (axillary), and the definition of raised temperature was dependent on the site of measurement (core >38°C, peripheral >38.4°C). In addition to the use of potentially poor substitutes for $T_{\text{brain}}$, the frequency of temperature measurement varied from hourly to six-hourly. In the event of a raised temperature, cooling interventions were not standardised. We have shown that the relationship between $T_{\text{brain}}$ during the first 48 hours following severe TBI and survival is complex. We demonstrated that those most likely to die had the highest and lowest mean $T_{\text{brain}}$ during the first 48 hours from injury. No association was found between the initial recorded temperature and survival (Childs et al. 2006). In another study examining the impact of a raised $T_{\text{brain}}$ (≥38.7°C) on neurochemistry and cerebral oxygenation in brain-injured (>50% had suffered a TBI) patients, the authors concluded that, during episodes of raised temperature, cerebral oxygenation was preserved and no signs of anaerobic metabolism were identified. They also stated that episodes of raised temperature were well tolerated when ischaemia was not the main pathophysiological mechanism and raised ICP was not a problem (Stocchetti et al. 2005). Similar findings have been reported by others (Spiotta et al. 2008).

**Patient Review (See 3.1)**

In the patient review carried out as part of this thesis over a one year period, no relationship between a raised temperature and an increased risk of death was uncovered. It is noteworthy that higher temperature or increased LoT temperature ≥38°C, at some time points, was in fact associated with a reduced risk of death.

Our data, together with the available literature, does not support the view that a raised temperature following a severe TBI is truly harmful. Although only one statistically
significant result was obtained from the review data, this suggests that a raised temperature may be associated with a decreased risk of death in our population of patients. In order to establish a definitive relationship between temperature and outcome a larger cohort of patients would be required. Despite lack of evidence that raised temperature is harmful, most ICU’s continue to place great importance in maintaining normothermia in patients with severe TBI. In an age of evidence based medicine it seems more important than ever to determine if avoidance of a raised temperature is indeed necessary.
4.3 Temperature Management Following Traumatic Brain Injury

The aim of temperature management on SRFT ICU is the maintenance of normothermia. A cooling protocol is in place to assist with temperature reduction (see 2.1.2).

During the observational element of this thesis I acted as an additional assistant at the bedside of each patient studied. I aided the patient-dedicated nurse with the tasks required to ensure the cooling processes followed protocol (sheet changes and gastric lavage). Without the assistance of the researcher it was likely that the cooling protocol would have been breached due to the other commitments of the patient-dedicated nurse. These sentiments were confirmed by personal communication with the nursing staff. The presence of a researcher may mean that the results obtained in the observational study do not reflect accurately the effects of cooling as routinely practiced. During the study it became clear that if labour intensive methods of temperature reduction continue to be employed, an additional member of staff should be available at the bedside to ensure the cooling protocol is followed. This has serious financial, staffing and rota planning implications for the unit but without this dedication the result will continue to be poorly executed cooling protocols.

Due to the intensive nature of the observational element of this thesis, researcher availability and exclusion of those patients that needed emergency surgery, small recruitment numbers were always expected. In total only 10 cooling episodes were studied in 5 patients. Three further patients were recruited but, one patient did not require cooling, one patient had cooling delivered that breached protocol as the patient was not sedated and the third patient had appropriate cooling delivered but the researcher was unavailable due to clinical on-call commitments.
4.4 Temperature Reduction following Traumatic Brain Injury

4.4.1 The Effect of Cooling on $T_{\text{brain}}$

Level-2 cooling did not reach target temperature on any of the three occasions it was studied and as a consequence the more aggressive method of temperature reduction (level-4) was subsequently required. Not only were target temperatures not achieved during these studied episodes but $T_{\text{brain}}$ actually increased from the starting temperature during each episode. Level 3 cooling was also studied on three occasions, twice in the same patient. On the two occasions it was studied in the same patient (patient 3), temperature targets were reached within the 5-hour study period. The third episode of level-3 cooling was stopped after 215 minutes, as the medical team did not feel that $T_{\text{brain}}$ was being adequately reduced in the face of ICP problems (patient 4). Level-4 cooling was initiated on four occasions, each time as a result of a failure of either level-2 or 3 to reach target temperatures. On three occasions target temperature was achieved.

4.4.2 The Effects of Cooling on $T_{\text{brain}}$ and Observed Significant Events

The two episodes of level 3 cooling studied that achieved target temperatures were in a patient who was critically ill and despite already having undergone a decompressive craniectomy continued to require a thiopentone infusion. During these studied level-3 episodes ICU clinicians provided extra input. They were particularly concerned with the large doses of noradrenaline the patient required to maintain MAP and the resultant marked peripheral vasoconstriction. This was significant for temperature reduction as on both occasions the patient received boluses of intravenous fluids in an attempt to counteract the peripheral vasoconstriction. A consultant intensivist who was present during the first episode of level-3 temperature reduction felt that this extra fluid might have assisted in reducing
peripheral vasoconstriction and as a result aid the temperature reducing effects of level-3. On both occasions, a thiopentone infusion had been running during and for many hours prior to the onset of cooling.

Level 4 cooling was stopped earlier than dictated by protocol on two occasions. During one episode the medical team stopped the cooling process early (temperature was within target values) as they believed that level-4 temperature reduction had contributed to a drop in serum sodium values due to the large volumes of fluid that the patient had absorbed. They also believed this then contributed to an unexpected rise in ICP that required medical intervention. In this case approximately 4 litres of ice cold water had been passed into the stomach over 130 minutes with only minimal aspirates. In another patient level 4 cooling was stopped by the medical team after only 70 minutes, although target temperatures had not been achieved. This was a result of spiralling rises in ICP, despite a thiopentone infusion commenced at the beginning of level 3 cooling. The patient underwent emergency surgery in the form of a decompressive craniectomy.

From the results obtained, Level-4 temperature reduction would appear to be the most effective method we have in our armamentarium. However, when we look at the rate of temperature reduction with level 4 cooling we see it is slow at reducing temperature to target levels. This coupled with the work intensive nature of this cooling level do not make it an appealing method of temperature reduction. In addition its use was felt to be contributing, at least in part, to the difficulties the treating team were experiencing with patient management on two occasions. Despite the possibility that these results were better than those that could be achieved without the assistance of a researcher, none of the methods of temperature reduction studied were effective or efficient. Not only were they time consuming for staff, but there is also a suggestion that they may not be completely innocuous, with some unexpected and undesirable consequences.
Why were these methods of temperature reduction not effective or efficient? Although this observational study was not designed to answer this question, there are a number of possible explanations. Firstly, were the patients in the study adequately sedated? In normal healthy volunteers, in whom a fever was induced, attempts to cool with air/water-blankets did not reduce the magnitude of fever compared with controls but did result in increased metabolic rate, activated autonomic nervous system and intense thermal discomfort (Lenhardt et al. 1999a). If TBI patients are not adequately sedated, particularly for surface cooling, these factors could result in heat production counteracting any potential heat loss. Level-2 temperature reduction does not involve the use of NMB and as a result any heat loss may be counter-acted by shivering thermogenesis. All of our methods of temperature reduction are susceptible to peripheral vasoconstriction and a subsequent reduction in peripheral heat loss. This may be compounded by the use of noradrenaline, which is frequently required in our patients. Finally, if we believe that the raised temperature we see, particularly in the early phase following TBI, is a true fever, the body will continue to defend its new set point and work against our attempts at temperature reduction. There is some evidence that the use of barbiturates may reduce $T_{\text{brain}}$ (Thorat et al. 2008). Patient 3 had a good reduction in $T_{\text{brain}}$ with level 3 cooling but a thiopentone infusion had been running for many hours prior to each studied episode. Thiopentone was commenced at the beginning of Patient 4’s cooling but no major reductions in $T_{\text{brain}}$ were observed.

In summary, none of the cooling levels observed during this study are efficient or effective at reducing $T_{\text{brain}}$ to maintain normothermia. Cooling was stopped earlier than dictated by protocol on several occasions by the treating clinicians, due to concerns that the cooling episodes were directly hindering patient management. As discussed, the presence of a researcher may have improved the results and other interventions (such as increased IV fluids as seen in patient 3) may have aided the cooling processes.
4.5 The Management of TBI

4.5.1 ICP

The management of ICP in the ICU setting following TBI is one of the cornerstones of therapy and there is a body of evidence to suggest that following a severe TBI raised ICP is independently associated with a poor outcome (Balestreri et al. 2006; Miller et al. 1981; Narayan et al. 1982; Treggiari et al. 2007). BTF guidelines suggest intervention with ICP thresholds >20mmHg (Anon. 2007). There is some clinical evidence to suggest that induced hypothermia may be effective in reducing raised ICP and improving outcome, even when conventional methods have failed (Polderman et al. 2002; Shiozaki et al. 1993; Zhi, Zhang, and Lin 2003). In the U.K. and Ireland, nine neurosurgical ICU’s proposed that they would introduce induced hypothermia in the event of a rise in ICP (Johnston et al. 2006). In our Neurosurgical ICU, normothermia is the target temperature in all TBI patients; hypothermia is not induced, even in the event of a raised ICP. As induced hypothermia has the potential to reduce a raised ICP, it was considered important as part of this study, to observe any changes in ICP during the cooling episodes commenced in the drive to maintain normothermia.

No consistent fall or general downward trend in ICP was noted in association with the studied cooling episodes but an increase or the addition of another sedating agent was required during some of these studied periods. During two (patient 1 and 2) out of the three studied level-2 episodes there were significant and unexpected rises in ICP which resulted in the need for increased sedation. In these cases the ICP was 10 and 12mmHg, respectively, higher at the end of the studied episode than the beginning. It should also be remembered that these changes in ICP were observed without any real reduction in \( T_{\text{brain}} \). During two episodes of level 3 cooling there was an increase in ICP. In one episode (patient 3) there was a very large rise towards the end despite the patient
being fully burst suppressed on EEG monitoring. It is unclear if this rise in ICP was part of the natural history of this particular patient, associated with other interventions (e.g. boluses of intravenous fluids) or even associated with the cooling process itself? As this patient died approximately 24 hours following this episode and had ongoing ICP issues, the rise seen during the second cooling episode seems most likely to be part of the natural history of this patient. The other rise in ICP during level 3 cooling (patient 4) was in a patient in whom there had also been difficulties with ICP control prior to the onset of cooling. However, a thiopentone infusion, which had previously been stopped, was recommenced at the onset of this level-3 cooling. During this studied episode there were five spikes of ICP greater than 25mmHg. This cooling episode was stopped early and converted to level-4 cooling as the treating physicians felt that the lack of significant temperature reduction was hindering the other measures in place to reduce ICP.

Changes in ICP were also noted during some of the studied level-4 cooling episodes. In one episode (patient 4), level 4 cooling was commenced earlier than dictated by protocol and was ceased, by the treating physicians, after only 70minutes due to spiralling rises in ICP. Level-4 cooling was particularly interesting in the study of patient 5. Despite a previously stable ICP there was a steady and unexpected rise in ICP to a level that required boluses of sedating agents and thiopentone. ICP fell rapidly following the medical interventions and cessation of cooling. Certainly in this case, as ICP had not been a previous problem, the treating physicians felt that the rise in ICP was as a direct result of the cooling process. As previously discussed one possible theory is that, absorption of water from the duodenum may have ultimately resulted in osmotic cerebral oedema leading to a rise in ICP.

Overall, there has been no observed trend towards ICP reduction in our attempts to maintain normothermia. At times there have been worrying rises in ICP, and although these could in some patients, have been attributed to the natural progression of the injury there are other
times when direct association with the studied cooling episodes seems likely. Further studies
would be required to provide a definitive answer. In the meantime it would be prudent for
treating clinicians to be aware of potential ICP changes with the methods employed to
maintain normothermia.

**BIS**

During preliminary work on ICU, several nurses commented that patients were not well
sedated, despite maximal sedation scores having been charted. One group demonstrated that
surface cooling in non-sedated healthy subjects, in whom a fever was induced, was a ‘thermal
discomfort’ (Lenhardt et al. 1999). This same group recommended that active cooling should
be avoided in unsedated patients. Bearing this in mind, ensuring that patients are adequately
sedated prior to the onset of surface cooling techniques would seem an issue of significance.
In order to examine this further a BIS monitor was applied to each patient during studied
cooling episodes. The treating physicians were blinded to BIS results during the studied
episodes.

Controversy continues to surround the use of BIS in TBI patients on Neurosurgical ICU.
However, as suggested by Deogaonkar et al., the trend in BIS index may be of greater value
in individual patient assessment than absolute BIS scores (Deogaonkar et al. 2004).

During level 2 cooling two patients were noted to at times have high BIS levels, in keeping
with the levels associated with light sedation. In contrast during the three studied level 3
cooling episodes BIS levels were much lower, in keeping with burst suppression as a result of
barbiturate coma and/or reduced brain activity as a result of severe injury. BIS levels were
more in keeping with deep sedation during level 4 cooling, except in patient 4 in which very
low levels were again noted.

From the observed changes in BIS values and clinical interventions, there is a possibility that
patient 1 and 2 were inadequately sedated prior to the onset of two studied level 2 cooling
episodes. Although the treating clinicians were blinded to the BIS values, their decision to add sedating agents as a result of changes in clinical parameters corresponded with high BIS values. These interventions also led to some reduction in BIS values. Level 2 cooling did not involve the use of NMB and EMG activity has been demonstrated to falsely elevate BIS values (Bruhn, Bouillon, and Shafer 2000). This needs to be considered when evaluating the results from level 2 cooling. Although the high BIS values seen in patient 1 and 2 may have in part been falsely elevated as a result of EMG activity, the BIS trend in conjunction with clinical findings do suggest inadequate sedation. This was further supported by the intervention of the treating physicians despite being blinded to the BIS values. The low BIS values seen in patient 3 and 4 were not surprising as a result of the degree of injury and ongoing barbiturate infusion leading to burst suppression. The large amount of time that the BIS value was 0 during cooling in patient 3 may have represented over-suppression due to the barbiturate coma however it may also have been an indication of approaching brain death (Vivien et al. 2002). Patient 3 died approximately 24 hours following the second episode of level 3 cooling. Patient 5 appears to have had steady BIS values during cooling despite the ICP changes seen towards the end of level 4.

From these observations there were two occasions when patients may not have been adequately sedated for level 2 cooling. This has important consequences not only as a noxious stimulus but also from a temperature reduction point of view. Potentially thermoregulatory defences cause shivering, peripheral vasoconstriction and increased metabolic rate counteracting any loss that may have been achieved by surface cooling (Lenhardt et al. 1999). It is therefore important for treating multi-disciplinary teams to be vigilant and to ensure adequate sedation prior to the onset of any of these cooling methods, particularly if the patient does not require neuromuscular blockade or a barbiturate infusion.
4.5.2 CPP

Following a TBI the maintenance of CPP is another cornerstone in patient management on ICU. Recent studies would suggest a target CPP in the region of 50-70mmHg and the avoidance of aggressive maintenance of CPP >70mmHg (Lin et al. 2008; Helmy, Vizcaychipi, and Gupta 2007; Anon. 2007). As a result of the deleterious nature of a low CPP following TBI, a vasopressor (noradrenaline) is frequently added by the treating clinicians to maintain a CPP within the recommended range. With regard to temperature reduction, the addition of vasopressors may be deleterious as a result of peripheral vasoconstriction and therefore a potential reduction of peripheral heat loss. During this study we observed the changes in CPP during each cooling episode and any changes in vasopressor administration.

During level 2 cooling CPP was higher than recommended without support in patient 2 and the beginning of the studied episode in patient 1. One possible explanation is that the application of wet sheets acted as a noxious stimulus, resulting in a high MAP and therefore high CPP. Prior to the onset of level 2 cooling a noradrenaline infusion was running in patients 5. Despite CPP being higher than recommended the noradrenaline infusion was continued with only minor adjustments. Patient 1 required a noradrenaline infusion during level 2 cooling, most likely as a result of increased sedation.

The maintenance of CPP in patient 3 was difficult, prior to the onset of cooling. During the first level-3 studied episode in patient 3 noradrenaline requirements rose slightly. During the second episode the requirements were very high but unable to maintain a CPP within target limits. Towards the end of this period the noradrenaline infusion was reduced, as a result of profound peripheral vasoconstriction, and a dobutamine infusion commenced. During the third episode of level-3 studied there were fluctuations in CPP that responded to ICP.
management and a noradrenaline infusion commenced prior to the onset of cooling was maintained at a steady level.

In three episodes of level-4 cooling the CPP was generally higher than recommended. One patient (patient 2) did not have any vasopressors running, in one patient vasopressors were stopped (patient 1) and in one reduced (patient 5). In one level 4 cooling episode (patient 4), in which ICP was increasingly difficult to control and CPP was falling, the noradrenaline infusion was actually reduced. This was also a result of profound peripheral vasoconstriction.

From our observations CPP trends were varied for each studied cooling episode. In some cases noradrenaline was commenced, most likely as a direct result of changes associated with the cooling processes. In other cases CPP was higher than recommended either with or without vasopressors support. Possible suggestions for this are that the patients are under sedated for the cooling process or that other interventions (such as the administration of boluses of IV fluids to counteract profound vasoconstriction as a result of cooling processes) may result in an increase in MAP and lead to a resultant increase in CPP. During the cooling episodes studied most cases required either vasopressor support to maintain CPP or CPP was higher than recommended targets.

4.5.3 The Avoidance of Secondary Brain Injury

*S100b*

As part of the observational study changes in the brain biomarker S100b were monitored throughout the whole period each patient was studied. S100b is established as a marker of brain injury and a recent update on protein biomarkers following TBI has concluded that only S100b has consistently demonstrated the ability to predict injury and outcome in adults (Kövesdi et al. 2010). However, there continues to be controversy surrounding the
interpretation of results, clearance characteristics and sample timing. From published studies there is no consensus regarding S100b levels that are reflective of outcome. However in a study of patients with severe TBI an initial serum level of 2.0µg/l or a secondary rise of more than 2.0µg/l or both was associated with a high mortality rate. This group also found that in patients, who survived, the highest serum S100b levels were found on day 1 and initial increases fell to baseline during a period of 2 to 6 days. The average time for S100b to return to baseline was 8 days in patients with severe disability, 5 days in patients with moderate disability and 2 days in patients with good outcome. It was thought that the average time for S100b to return to normal levels reflected the duration of secondary damage. It should be noted that initial samples were taken at between 2 and 40 hours following injury (Raabe et al. 1999). Other studies have suggested that the peak in serum S100b may not occur until day 2 (Elting et al. 2000; Ucar et al. 2004). Another group demonstrated different patterns of S100b release in patients with severe TBI; with an admission GCS of 6-8 compared to admission GCS of 3-5, one month survivors compared to non-survivors and in patients with pupils that were bilaterally fixed and dilated, unilaterally fixed and dilated or both reactive (Korfias et al. 2007). The timing of serum sampling is clearly important but the lack of definitive release and decay characteristics of S100b following TBI adds further to the confusion surrounding the interpretation of results. Raabe et al suggested that observing the time course of S100b may be more clinically useful and that increasing or persistently high levels could indicate ongoing damage despite therapy, whereas quickly decreasing levels or persistently lower levels (<0.5µg/l) may indicate no relevant secondary damage (Raabe et al. 1999). Another group demonstrated that S100b was significantly higher in patients with secondary neurological complications compared to patients without, on the day of the complication and the day after. They did not find any difference the day prior to the complication; however samples were only taken on a daily basis (Undén et al. 2007).
Bearing this in mind when we observe the S100b results obtained for each studied patient we see that initial sampling was performed between 5 and 22.5 hours from injury. Two patients (patient 3 and 4) had initial levels of 2.0µg/l or above. Patient 3 died and patient 4 had a poor outcome (GOS 2). Patient 1 also died and although serum S100b were initially <2.0µg/l, levels soon rose to 3.32µg/l. Two patients (patient 5 and 7) had S100b levels persistently <0.5µg/l and had good outcomes (GOS 4 and 5 respectively).

Observing temporal changes in S100b each patient had a differing pattern of clearance. During cooling rises were noted in one level 2 episode and two level 4 episodes. Rises in S100b, not associated with cooling, were also seen in patient 3, 4 and 6. In patient 3 levels increased at a point that corresponded with a period of increasing instability, with rising ICP and falling T\textsubscript{brain}, despite maximal medical therapy. The sample was taken only 5.5 hours before the patient underwent a decompressive craniectomy. Interestingly, S100b levels were lower on return from theatre (1.05µg/l) and continued to fall, even during studied cooling episodes, until the sample rose again at 116 hours from injury (1.72µg/l). This was taken during a period of clinical deterioration and only 1 hour before the patient died. Patient 4 demonstrated a rise in S100b at the beginning of the study period, which corresponded with a period of slightly raised temperature that settled rapidly without intervention and also a raised ICP that also settled following increased sedation and the start of a thiopentone infusion. A small rise in serum S100b levels was also observed in patient 6 at 37 hours from injury. This did not correspond with a raised T\textsubscript{brain}, cooling episode or difficulties managing ICP or CPP, but did occur shortly after the patient had sedation and noradrenaline switched off.

Overall, in the small cohort of patients studied changes in S100b were observed that could be representative of secondary brain injury. In association with cooling, a large rise in serum S100b was observed in patient 1 during a studied level 2 cooling episode and a smaller rise during level 4 cooling. A small but definite rise during a level 4 studied episode was also
observed in patient 2. Although this study was not designed to determine cause and effect, the possibility that these cooling methods may be associated with secondary brain injury needs to be considered. Other rises were seen not in association with cooling, such as prior to decompressive craniectomy and death in patient 3 and in the early period of patient 4’s admission, corresponding to a period of ICP instability.

However, it is important to consider some issues surrounding these observations. Firstly, some may suggest that the early rises in S100b seen in patient 1, 2 and 4 resulted as S100b had not reached its peak at the time of the initial samples. In these three patients the initial samples were taken within 14 hours of injury. The suggestion from available literature is that serum S100b levels following TBI may not peak until one to two days following injury (Elting et al. 2000; Raabe et al. 1999; Ucar et al. 2004). Other rises were seen in S100b beyond the initial 24 hours following injury and from the literature it would seem that any failure to decay towards normal may be indicative of secondary injury. As a result can it be assumed that any rise, no matter how small, in S100b levels may indicate ongoing injury? Furthermore, although the half-life of S100b is 2 hours, in severe TBI it is continued to be released in the days following injury, unlike minor head injury (Raabe et al. 1999; Rothoerl et al. 1999). In this study S100b was sampled every 12 hours during the study period (more frequently during studied cooling episodes) and as a result it is difficult to know if other rises in S100b have been missed. Due to the complex nature of all ICU patients other events and variables that have not been broached by this observational study, may have influenced the results.

**Inflammatory Markers**

Throughout the study period serum samples were also tested for levels of IL-6 and TNF-α. From the literature it would appear that IL-6 has a major role to play in repair and in regulation of inflammation in the injured brain (Ziebell and Morganti-Kossmann 2010;
Morganti-Kossmann et al. 2001). TNF-α appears to have a bi-phasic action, with early neuroinflammatory and late neuroregenerative roles (Ziebell and Morganti-Kossmann 2010). For the purposes of this study these inflammatory markers were monitored to observe changes throughout the study period but particularly during studied cooling episodes. From the observed results it is clear that the pattern of serum IL-6 and TNF-α detection was different for each patient although, there was a general trend for IL-6 to fall and TNF-α to increase during the study period. Looking more closely at changes during cooling, increases in IL-6 levels were seen in all three level 2 cooling episodes. Conversely, TNF-α remained stable in patient 1 and 5 but a large increase in level was observed early during level 2 cooling in patient 2. In the three studied level 3 cooling episodes, IL-6 rose during the two studied episodes in patient 3 but remained stable in patient 4. During the second studied level 3 episode in patient 3 TNF-α levels fell but remained stable during the other studied level 3 episodes. During level 4 cooling only patient 1 demonstrated a rise in IL-6, while rises were seen in TNF-α in both patient 1 and 2.

Other changes were observed outside the studied cooling episodes. In patient 1 IL-6 reached a further peak 42 hours from injury. This sample was taken 5 hours following the commencement of noradrenaline to maintain CPP and 2 hours following a period of increasingly difficult to control ICP. Patient 2 had a large surge in IL-6 in two samples taken at 77.5 and 89.5 hours from injury. This occurred during a time when noradrenaline had been commenced for low CPP, thiopentone had been commenced for refractory ICP and patient oxygen requirements were increasing due to a proven chest infection. Patient 3 had a large rise in IL-6 towards the end of the study period, at a time of rising ICP and falling CPP despite maximal medical therapy. Patient 4 had a further peak in IL-6, 108 hours from injury, approximately 15 hours following an emergency decompressive craniectomy. Rises were also seen in both IL-6 and TNF-α towards the end of the study period in patient 5. This
corresponded to a period of protocol breach, when a level 2 cooling episode was delivered while the patient was not sedated.

Changes in mainly IL-6 but also TNF-α have been observed throughout cooling episodes and the entire study period. It is difficult with such a small cohort and varying pattern of values to interpret these results, except to say that changes in both cytokines have been observed during times when ICP and CPP levels required intervention and also during an episode of surface cooling without sedation. Changes were also observed during studied cooling episodes. A further study with a larger number of patients would need to be performed in order to establish any true link between these cooling methods and inflammation. Serum sampling occurred every 12 hours (more frequently during cooling) and therefore it is unclear if the pattern of cytokine release may have appeared different with more frequent sampling. Many variables contribute towards outcome on ICU. Due to the nature of this study many of these variables will not have been measured and as a result it is unclear if these may have influenced the results.

Over the last decade some research groups have focused on the development of novel therapeutics to specifically target inflammation following TBI. It is hoped that the development of such agents will ultimately result in improved outcome following TBI by manipulating secondary injury cascades. The promising results of such therapeutic agents in animal models have not translated to the bedside (Edwards et al. 2005; Maas et al. 2006). Indeed the use of corticosteroids following TBI is not recommended following a large double-blind randomised placebo-controlled trial of the effect of early administration of a corticosteroid following TBI. This study showed an increase risk of death or disability in the corticosteroid group (Edwards et al. 2005). Currently, the use of non steroidal anti-
inflammatory compounds is under investigation, in experimental models of TBI. To date the results have been ambiguous (Ziebell and Morganti-Kossmann 2010).
4.6 The Future of Temperature Management Following Traumatic Brain Injury

Our observational study was devised due to consensus from the ICU staff that the methods employed to maintain normothermia were time consuming and inefficient. There was also a suspicion that these methods were not as innocuous as they are often assumed to be. As a result, there was an agreement that further work was required to observe the effects of our cooling methods, specifically on $T_{\text{brain}}$ and also to observe for changes in parameters that were pertinent to the management of TBI patients. As a result ICP (and changes to sedation requirements), CPP (and changes to noradrenaline requirements), BIS, S100b and the cytokines IL-6 and TNF-\(\alpha\) were all monitored during the study period and more closely during studied cooling episodes. Depending on the issues highlighted, this observational work was to provide the basis of future study planning.

Despite the small number of cooling episodes studied, along with the possibility that the presence of a researcher enhanced the adherence to protocol, some observations were made upon which further studies could be based. All cooling methods employed were time consuming and inefficient. Level 2 cooling was particularly ineffective, with $T_{\text{brain}}$ rising above the starting value in each studied episode. Although this study was not designed to determine cause and effect, adverse changes in ICP and CPP were observed which may have been related to the cooling processes. Although more difficult to interpret, changes in S100b and cytokines were also observed during cooling episodes, as were worrying trends towards under sedation on at least two occasions.
4.6.1 Recommendations for Clinical Practice from this Research

These findings were observed as part of an ongoing drive to maintain normothermia, although there is little evidence to support this notion. Going back to basics, it seems that even the definition of what a ‘normal’ temperature is or the classification of an abnormally elevated temperature is unclear. The generally accepted definitions of 37°C (‘normal’) and 38°C (‘fever’) are outdated and is further confounded by the source of temperature readings – peripheral, core or brain. As previously mentioned, other definitions of ‘fever’ have been used including; an oral, rectal or central temperature of ≥38.3°C or a T$_\text{brain}$ ≥38.7°C (O’Grady et al. 1998; O’Grady et al. 2008; Stocchetti et al. 2005). One of these groups also arbitrarily defined normal T$_\text{brain}$ as 38°C (Stocchetti et al. 2005). Although there is no clear evidence that T$_\text{brain}$ is 0.4 °C higher than core temperature (although this appears to be the middle ground from studies looking at core versus brain temperature) or that normal T$_\text{brain}$ is 38°C, these definitions, along with those of the Society of Critical Care Medicine, seem more appropriate than the generally accepted values.

There are concerns that a raised temperature may be harmful following TBI and the debate surrounding the use of induced hypothermia continues. This controversy along with a lack of consensus throughout neurosurgical ICU’s in the UK and Ireland needs to be addressed. One of the first steps would be to set up a working group with the aim of standardising current practices with regards to the fundamentals of temperature management, based on available evidence. How should temperature be measured in TBI patients? How often does it need to be measured? Can an agreement be reached to abandon the outdated but routinely used temperature thresholds? Can a fresh approach to temperature, based on individual patient requirements be implemented? I believe that a consensus with regards to these questions would be a stepping stone in the search for answers to the other issues surrounding
temperature management in TBI patients. It may even provide the foundations to begin collaborative research in this field.

The focus of the discussion has been on the management of temperature following TBI in the ICU setting however, if a standardised approach was to be considered, the early management of temperature in the trauma setting, district hospital and during transfers may also need to be addressed.

I do not think that an agreement surrounding temperature targets or methods of temperature reduction would come easily. Even in our own unit unease remains regarding a raised temperature following TBI, despite little evidence base for its association with poor outcome. There is a general acknowledgement that induced hypothermia is not supported by clinicians at present. The methods currently used to reduce temperature are time consuming and inefficient. From the literature the use of a catheter-based cooling system has had promising results with a similar side effect profile to a conventional central venous catheterisation (Diringer 2004; Puccio et al. 2009; Schmutzhard et al. 2002). Rapid cooling was also achieved using an infusion of refrigerated intravenous fluids in conjunction with a water cooling blanket. The temperatures fell rapidly using the refrigerated fluids and the temperature was maintained at this lower level using the water cooling blanket (Polderman et al. 2005).

Guidelines

It is difficult to create guidelines for the management of temperature in TBI patients on ICU due to the unresolved issues and ongoing controversies. However, following consideration of the literature available and study observations, I have put together some suggestions surrounding the management of temperature in patients with severe TBI in the ICU setting:

- $T_{\text{brain}}$ is the gold standard of temperature measurement. If this is not a viable option then core measurements should be used. The treating clinicians should be aware of
the inherent problems with each of these methods and the potential for core
temperature to inaccurately reflect $T_{\text{brain}}$, particularly at times of temperature flux.
Skin fold, oral and tympanic measurements should not be used.

- Brain and core temperature can be displayed continually. However, an hourly
  recording should at least be made.

- Temperature should be considered elevated if core readings are $\geq 38.3^\circ\text{C}$ or brain
  readings are $\geq 38.7^\circ\text{C}$.

- If temperature is elevated the decision to intervene should be made on an individual
  patient basis. Factors which need to be considered include; age, medication, co-
morbidities, other injuries and co-morbidities. Temperature reduction should be
  considered if there is evidence of; haemodynamic instability, refractory ICP, CPP that
  is difficult to maintain or other features of concern.

- If intervention to reduce temperature was necessary then again a decision regarding
  target temperature should be made on an individual patient basis. If there was
  evidence of a refractory ICP then mild hypothermia should be induced. Otherwise,
  temperature should be reduced to a level considered ‘normal’ for that patient.

- If available temperature reduction should be achieved using an intravascular cooling
  device. If this is not available a reasonable alternative would be the infusion of
  refrigerated intravenous fluids to rapidly decrease temperature followed by
  maintenance using available conventional methods. Potential side effects of the
  cooling processes and mild hypothermia must be considered.

- If mild hypothermia was induced as a result of refractory ICP there is some evidence
  it should be continued for 5 days. Rewarming should be slow.
The very nature of these suggestions highlights the ongoing need for better information.

Even without major new evidence or changes to practice, if the currently accepted levels of ‘normal’ and ‘fever’ were abandoned, then many potentially unnecessary cooling interventions may be prevented. Due to the findings of this observational study and the potential for concerning changes during the cooling episodes, evidence is required to determine if a raised temperature is truly harmful following TBI. This may be difficult to establish due to the multiple confounding factors that contribute to outcome and small patient numbers. However, I believe the next step in this debate would be to carry out a randomised controlled trial examining outcome in TBI patients, with one group exposed to our standard normothermia protocol and a second group that does not receive temperature intervention (except perhaps at very extremes of temperature). It may be possible to increase patient numbers by collaborating with other units. The results from such a study may not yield all the answers surrounding a raised temperature following TBI, but it may suggest if striving to maintain normothermia using our current cooling methods is better or worse for our patients when compared to no intervention.

Multiple laboratory and clinically based investigations are required to unlock the enigma of brain temperature management following TBI. There is still much to be answered in the field of temperature following TBI and the possibilities of maintained normothermia and induced hypothermia. It is difficult to imagine a future in which secondary injury following TBI can be modified, when so many questions surrounding temperature and TBI remain unanswered. However, the future may lie in the development of novel pharmaceutical therapies to manipulate secondary injury. In the meantime the development of novel devices, such as a reliable and non-invasive device to measure \( T_{\text{brain}} \) or a safe, efficient and effective device to reduce temperature would greatly aid the community involved in temperature management following TBI.
4.7 Conclusions

Temperature management following TBI remains contentious, with no consensual approach throughout the UK and Ireland. Even the fundamental issues surrounding ‘normal’ temperature and ‘fever’ are unresolved. In this thesis there was no evidence of an increased risk of death with a raised temperature in the population of patients studied. The observational element demonstrated that the cooling methods used to maintain normothermia were often time-consuming, inefficient and ineffective. There were also some concerning changes in monitored biochemical and physiological parameters during cooling episodes. At present there is no clear evidence that induced hypothermia is of benefit and due to ongoing concerns regarding raised temperature following TBI the middle ground of normothermia is often sought. Further studies are required in order to establish the true nature of raised temperature in the early stages following TBI and whether this may result in increased secondary brain injury. Any potential benefit of induced hypothermia also needs to be clearly established. With this knowledge management could be targeted appropriately. Temperature reduction methods continue to be used throughout the UK and Ireland, mainly on the maintenance of normothermia. Until further evidence becomes available, clinicians need to be aware of the potential pitfalls of commonly used temperature reduction methods. Further studies need to be performed to establish possible links with cooling and detrimental changes in physiological and biochemical parameters following TBI.
4.8 Post Script

The results of the National Acute Brain Injury Study: Hypothermia II have now been published (Guy L Clifton et al. 2011). This was a randomised multi-centre clinical trial of younger patients (16-45 years) with severe TBI enrolled within 2.5 hours of injury. The patients were either assigned to the hypothermia group or normothermia group. In the hypothermia group temperature was reduced early following injury (mean of 2.6 hours to reach 35°C and a mean of 4.4 hours to reach 33°C) and maintained at 33°C for 48 hours, before being rewarmed by 0.2°C/hr. The primary outcome measure GOS at 6 months.

As a result of concerns regarding slow patient recruitment in addition to patient safety, an interim analysis was carried out earlier than planned. Patient safety concerns had been heightened by a randomised clinical trial that reported weak evidence of an adverse outcome in children with severe TBI treated with hypothermia (Hutchison et al. 2008). Interim analysis did not reveal a significant difference in outcome between patients treated with hypothermia and normothermia. In addition the hypothermia group experienced more episodes of raised ICP, thought to be due to the aggressive methods used to avoid hypotension. Following this interim analysis the trial was stopped for futility.

This well designed randomised controlled trial has further demonstrated a lack of evidence for the use of induced hypothermia as a prescriptive treatment for all patients with severe TBI. In conjunction with the previously published randomised controlled trials discussed in this thesis, there is no evidence that the use of induced hypothermia in patients following a severe TBI improves outcome. Some may argue that the low number of patients enrolled at the time of interim analysis and the short fixed time period of induced hypothermia means that this study does not put an end to the use of hypothermia in TBI (Andrew Maas and Nino Stocchetti 2011). I believe that this body of evidence means that hypothermia should no
longer be used as a prescriptive treatment for all patients following TBI and that any future trials should focus on the induction of hypothermia for targeted individual need.
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**APPENDIX**

Appendix A

*Glasgow Coma Scale*

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<th>Eye Opening</th>
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</tr>
<tr>
<td>Eye opening to speech</td>
<td>3</td>
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<tr>
<td>Eye opening to pain</td>
<td>2</td>
</tr>
<tr>
<td>No eye opening</td>
<td>1</td>
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<th>Motor Response</th>
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<tr>
<td>Obeys commands</td>
<td>6</td>
</tr>
<tr>
<td>Localising response to pain</td>
<td>5</td>
</tr>
<tr>
<td>Withdrawing to pain (Normal flexion)</td>
<td>4</td>
</tr>
<tr>
<td>Flexor posturing to pain (Abnormal/spastic flexion)</td>
<td>3</td>
</tr>
<tr>
<td>Extensor posturing to pain</td>
<td>2</td>
</tr>
<tr>
<td>No motor response</td>
<td>1</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Verbal Response</th>
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<tbody>
<tr>
<td>Orientated speech</td>
<td>5</td>
</tr>
<tr>
<td>Confused speech</td>
<td>4</td>
</tr>
<tr>
<td>Inappropriate speech</td>
<td>3</td>
</tr>
<tr>
<td>Incomprehensible sounds</td>
<td>2</td>
</tr>
<tr>
<td>No vocal response</td>
<td>1</td>
</tr>
</tbody>
</table>
Appendix B

Associated Problems with Core Temperature Measurements

<table>
<thead>
<tr>
<th>Method of Measurement</th>
<th>Problem</th>
</tr>
</thead>
</table>
| Rectal                | Probe is easily dislodged  
|                       | Can be insulated from surrounding tissues by faeces |
| Bladder               | Sensor is influenced by urinary flow |
| Nasopharyngeal        | Can cause nasopharyngeal bleeding  
|                       | Temperature reading depends on the depth of the probe |
| Oesophageal           | Temperature reading depends on the depth of the probe |
| Tympanum              | Sensor does not always abut the tympanum  
|                       | Cerumen or dried blood in auditory canal can lead to a delay in response time |
Appendix C

Clinical Paper: Body Temperature Management after Severe Traumatic Brain Injury

Body temperature management after severe traumatic brain injury: Methods and protocols used in the United Kingdom and Ireland

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Received 9 December 2005; accepted 14 February 2006

Keywords
Brain injury; Temperature; Intensive care

Summary
Objective: To establish whether there is consensus in the management of body temperature in patients with severe traumatic brain injury (TBI) admitted to hospitals in the United Kingdom and Ireland for neurosurgical intensive care.
Methods: Permission was granted from the Society of British Neurosurgeons (SBNS) and the Local Research Ethics Committee to undertake the survey. A senior member of nursing staff from all adult neurosurgical units, excluding our own, was contacted by telephone.
Results: All 33 adult neurosurgical centres participated. Six units had a formal written protocol for the management of body temperature. For the remainder (27 units), interest was expressed in a protocol for temperature management particularly for those patients with intractable hyperthermia fever. Administration of the antipyretic paracetamol was the most common ‘first-line’ treatment (13 units). Other ‘first-line’ methods were: circulating air-cooling blankets (9 units), water-filled cooling blankets (6 units), targeted sponging or wet sponges (17 units), convection fans (2 units) and administration of cold fluids via the gut or circulation (1 unit). When ‘first-line’ methods failed to bring about a fall in temperature, different combinations of these methods were used.
Conclusions: From this survey, it is evident that there is no consensus in the approach to temperature management in neurosurgical intensive care patients with severe TBI. Review and rationalisation of systems of care may be required in an effort to develop evidence-based national and international guidelines.

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* A Spanish translated version of the summary of this article appears as Appendix in the online version at 10.1016/j.resuscitation.2006.02.010.
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doi:10.1016/j.resuscitation.2006.02.010
Appendix D

Regions of Greater Manchester Served by SRFT
Appendix E

Glasgow Outcome Scale

1  DEAD

2  VEGETATIVE STATE
Unable to interact with environment; unresponsive

Patients who show no evidence of meaningful responsiveness. Patients who obey even simple
commands, or who utter any words, are assigned to the better category of severe disability. Vegetative
patients breathe spontaneously, have periods of spontaneous eye-opening when they may follow
moving objects with their eyes, show reflex responses in their limbs (to postural or painful stimuli),
and they may swallow food placed in their mouths. This non-sentient state must be distinguished from
other conditions of wakeful, reduced responsiveness--such as the locked-in syndrome, akinetic
mutism and total global aphasia.

3  SEVERE DISABILITY
Able to follow commands/ unable to live independently

This indicates that a patient is conscious but needs the assistance of another person for some activities
of daily living every day. This may range from continuous total dependency (for feeding and washing)
to the need for assistance with only one activity--such as dressing, getting out of bed or moving about
the house, or going outside to a shop. Often dependency is due to a combination of physical and
mental disability--because when physical disability is severe after head injury there is almost always
considerable mental deficit. The patient cannot be left overnight because they would be unable to plan
their meals or to deal with callers, or any domestic crisis which might arise. The severely disabled are
described by the phrase "conscious but dependent."

4  MODERATE DISABILITY
Able to live independently; unable to return to work or school

These patients may be summarized as "independent but disabled," but it is perhaps the least easily
described category of survivor. such a patient is able to look after himself at home, to get out and
about to the shops and to travel by public transport. However, some previous activities, either at work
or in social life, are now no longer possible by reason of either physical or mental deficit. Some
patients in this category are able to return to certain kinds of work, even to their own job, if this
happens not to involve a high level of performance in the area of their major deficit.

5  GOOD RECOVERY
Able to return to work or school

This indicates the capacity to resume normal occupational and social activities, although there may be
minor physical or mental deficits. However, for various reasons, the patient may not have resumed all
his previous activities, and in particular may not be working.
Appendix F

Information for Patient Relatives

Research Study: Raised brain temperature - systemic and cerebral responses

Introduction

High brain temperature is common after a head injury. To treat this, we give a drug which lowers body temperature and cool the surface of the body. Sometimes the treatments we use are slow to take effect. Sometimes one treatment will work better in one patient than in another. We want to try to understand how the body responds to our cooling treatments by studying the body and brain responses to a rise in temperature and the how the body responds when we try to lower temperature. To do this we will closely monitor your relative, taking note of the changes in, for example, heart rate, blood and brain pressure. We will also take blood samples and use new techniques, as they come along, to help us find the answer.

What measurements will be made?

1. We will measure **body and brain temperature**. A sensor which measures brain pressure and temperature is inserted by a neurosurgeon when your relative arrives in the intensive care unit (ICU) and is a part of routine monitoring after a head injury. In this study we will document body and brain temperature throughout your relatives stay in ICU.

2. We will also assess **level of consciousness**. This can be achieved quite simply by placing a sensor over the forehead. The monitor is called a BIS monitor and works by measuring brain activity (EEG). In ICU it is normal practice to give drugs to ensure that patients are sedated and pain free so that they do not become distressed after their injury. This treatment also influences the level of consciousness. The BIS monitor will help us in assessing conscious level during cooling treatments.

3. **Extra blood samples** are needed in this study. This is necessary so that we can measure markers of body inflammation and brain tissue injury. These proteins are called IL-6, TNF and S100. We will need to take some blood samples every day but when body cooling is in progress more frequent blood sampling will be needed. In total the amount of blood taken over the 5 days of the study is about 150 ml. This is equivalent to half a coffee mug.

4. In some, but not all patients, we will also **measure brain oxygenation and blood flow**. This measurement is also made from a sensor placed over the side of the head. These measurements are made by shining near infrared light into the head. Some of this light is absorbed by oxygen carrying pigments (haemoglobin for example) whilst most is reflected back to the forehead sensor. The measurements are obtained from a near infrared spectrophotometry (NIRS) monitor. To measure brain blood flow a very small amount of a ‘dye’ is injected into a vein cannula (no needle prick necessary) and the amount of light absorbed by the dye aids calculation of the rate of blood flowing to the brain.
Continued- Information Sheet for Relatives

What are the possible risks?
BIS monitor- there are no risks in using the monitor. This monitor is used routinely when patients are asleep during an operation. Sometimes a small red mark appears on the skin after removing the sensor but this fades after 20-30 min.
Extra blood samples- the amount of blood we will need over the course of this 5 day study is not expected to cause any problems for an adult patient. In total this will be no more than a half teacup of blood over a 5-day period.
Near infrared spectrophotometry- Since not all patients will have NIRS monitoring in this study this section may not apply to you. However if your relative does receive NIRS monitoring for assessment of brain oxygenation and blood flow we will need to administer a small amount of a dye called indocyanin green to help us detect the rate of blood flow to the brain. It is rare for a reaction to the dye to occur and it is used widely and routinely in cardiac patients.

Are there any benefits for my relative?
There are no direct benefits to your relative from this study but the results will help us to understand the effects of our treatments so that other patients with a similar injury may benefit in the future.

Does my relative have to take part in this study?
No, your relative does not have to take part in this study. If you do not wish your relative to take part, you do not have to give a reason. The doctors will not be upset, and the treatment will not be affected. However if your relative does take part, but later you change your mind, you can withdraw your relative from the study at any time.

Thank you for taking the time to read this information sheet. If you have any further questions a member of the study team will be very happy to come and answer these for you. Please do not hesitate to contact us at any time.

You can contact us at any time.

Dr Charmaine Childs 07623 620 346
Ms Nicola Johnston 07623 604 294
Appendix G

Components of the Camino Intracranial Pressure-Temperature Monitoring Kit (Model 110-4BT)
Appendix H

Manufacturer’s Instructions for the Insertion of Camino Intracranial Pressure-Temperature Monitoring Kit

- The insertion site was chosen (usually right frontal) and prepped and draped in a sterile fashion
- The incision site (2-3cm anterior to the coronal suture in the mid-pupillary line) was infiltrated. An approximately 0.5cm incision was made and carried to the bone (Figure H1)

![Fig. H1. Incision site](image)

Note – not all neurosurgeons advocate shaving hair as demonstrated in Fig. H1.

- Using a hand held twist drill the accompanying drill bit was secured with the safety stop at the desired level
- A twist drill hole was made through the inner and outer tables of the skull
- The dura was then opened in a cruciate fashion using an 18G spinal needle and a stylet inserted to ensure adequate opening.
- A Camino bolt was screwed manually into the skull (seating at the surgeons discretion)
- The stylet was inserted through the bolt to clear the passage (Fig. H2)

![Fig. H2. Positioning of bolt and clearance of passage](image)

- The Camino catheter was removed from its sterile packaging and the transducer connector firmly attached to the preamp connector of the display monitor
- The reading was adjusted to zero using the zero adjustment on the bottom side of the transducer connector (Figure H3)

![Fig. H3. Zero adjustment](image)

- To display the temperature on the host monitor the Camino thermistor connector was connected to the cardiac output monitor cable
• The Camino catheter was inserted into the bolt. The surgeon placed his fingers between the 6 and 7cm marks and inserted the catheter until his fingers touched the top of the bolt. At this point the tip of the catheter is be 2cm beyond the bolt into the parenchyma

• The catheter was then pulled back slightly and the compression cap of the bolt turned clockwise to secure the catheter in place (Fig. H4)

Fig. H4. Insertion of catheter

• The strain relief sheath was secured onto the compression cap (Fig. H5)

• The red depth indicator should not be visible above the strain relief

Fig. H5. Securing the strain relief gauge
Appendix I

BIS Equipment and Bedside Set-up

The patients’ forehead was exposed
The exposed skin was then cleaned with an alcohol wipe and allowed to dry
The sensor, which consists of four sensor elements, was placed diagonally across the forehead (Fig. I2)
- Sensor element 1 – At the centre of the forehead, approximately 5cm above the bridge of the nose
- Sensor element 4 – Directly above the eyebrow
- Sensor element 3 – On the temple, between corner of eye and hairline

Fig. I1. BIS monitoring equipment

BIS Bedside Monitoring Set-up:
Fig. I2. Position of the four sensor elements

- The edges of the sensor were pressed to achieve firm contact with skin
- All sensor elements were then pressed firmly for five seconds
- The sensor tab was inserted into the patient interface cable (Fig. I3)

Fig. I3. Insertion of sensor tab into PIC

- Using the attachment clip the Digital Signal Converter (DSC) was secured to a convenient location near the patients head.
The monitor was switched on and a sensor check automatically initiated. The possible results of the sensor check were:

- **Pass** - An electrode passes if the impedance for that electrode is less than 7.5 kilo ohms
- **High** – An electrode is labelled high if its impedance value is above 7.5 kilo ohms. As long as the combined impedance of elements one and three and one and four is less than 15 kilo ohms, the sensor check will be considered successful.
- **Noise** – This appears if the signal from the electrode goes beyond the measurable range

If the sensor check was unsuccessful all electrodes and connections needed to be re-checked.

Once the sensor check had been completed monitoring began and the appropriate information appeared on the screen (Fig. I4)

![Figure I4. BIS trend screen](image)

- Once the cooling protocol was complete the sensor was disconnected from the PIC and gently removed from the patient’s forehead. The sensor was discarded. The forehead was cleansed and allowed to dry
Appendix J

Additional BIS Parameters, DSC Specifications and EEG Specifications

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Description</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signal Quality Index (SQI)</td>
<td>A measure of the signal quality for the EEG channel source that is calculated based on impedance data, artefact and other variables</td>
<td>0-100</td>
</tr>
<tr>
<td>Electromyography (EMG)</td>
<td>The absolute power in the 70-110Hz range. The power value is reported in dB with respect to 0.0001µV²</td>
<td>30-80dB Trend</td>
</tr>
<tr>
<td>Suppression ratio (SR)</td>
<td>The percentage of epochs in the past 63 seconds in which the EEG signal is considered suppressed</td>
<td>0-100%</td>
</tr>
<tr>
<td>Spectral Edge Frequency (SEF)</td>
<td>The frequency at which 95% of the total power lies below it and 5% lies above it</td>
<td>0.5-30Hz</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Digital Converter Specifications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Analog to digital converter</td>
<td>Noise-shaped sigma-delta</td>
</tr>
<tr>
<td>Sampling rate</td>
<td>16 384 samples/sec</td>
</tr>
<tr>
<td>Resolution</td>
<td>16 Bits at 256 samples/sec</td>
</tr>
<tr>
<td>Input Impedence</td>
<td>50 Mohms minimum</td>
</tr>
<tr>
<td>Noise</td>
<td>&lt;0.3*V RMS 0.25Hz to 50Hz</td>
</tr>
<tr>
<td>Isolation Mode</td>
<td>110dB at 50/60Hz to earth Ground</td>
</tr>
<tr>
<td>Bandwith</td>
<td>DSC-2: 0.16 to 800Hz  DSC-XP: 0.16 to 450 Hz</td>
</tr>
<tr>
<td><strong>EEG Specifications</strong></td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>---</td>
</tr>
<tr>
<td><strong>Epoch Duration</strong></td>
<td>2 seconds</td>
</tr>
<tr>
<td><strong>Artifact Rejection</strong></td>
<td>Automatic</td>
</tr>
<tr>
<td><strong>EEG Scales</strong></td>
<td>25*V/div (+/-1mV Full Scale)</td>
</tr>
<tr>
<td><strong>EEG Sweep Speeds</strong></td>
<td>25mm/sec</td>
</tr>
</tbody>
</table>
| **Update Rate**         | 1s for BIS Index  
                         | 10s for Trend  |
| **Filters**             | On - 2to70Hz  
                         | Off - 0.25 to 100Hz |
Appendix K

Arterial Line Sampling Protocol

1. Prepare equipment. This will include:
   - clean receiver
   - 2 x 5 ml sterile syringes
   - sterile white cap
   - sterile disposable glove
   - sterile gauze
   - alco wipe

2. Check the limb with arterial line in situ. Observe colour and temperature. If cold or mottled do not proceed with sampling. Contact medical team for advice.

3. Check the arterial line tracing on the bedside monitor. If trace is inadequate do not proceed with sampling. Seek medical advice.

4. Wash and dry your hands.

5. Open syringes alco wipe and cap into receiver.

6. Put on sterile gloves and use the sterile paper from the glove to place under the sampling port of the arterial line.

7. Remove the white cap from the sampling port and cleanse using the alco wipe. Attach a 5 ml syringe.

8. Turn the tap so that it is off towards the heparin flush and open towards the patient.

9. Gently withdraw 5ml of blood. Stop if blood not flowing easily or if limb blanches – seek medical advice. Turn the tap so that it is off to all ports.

10. Discard the 5ml blood sample and place another 5 ml syringe into sampling port.

11. Turn tap so that it is off towards the heparin flush and open towards the patient.

12. Withdraw 5 ml/2 ml of blood (according to the protocol). Stop if blood not flowing easily or if limb blanches.

13. Turn the tap off towards the sampling port and open towards the patient and flush. Remove the syringe. Flush the arterial line until the line is clear of blood. Check the arterial line tracing.

14. Turn the tap so that it is off towards the patient and open towards the sampling port. Flush onto the gauze until the port is clear of blood.

15. Turn the tap so that it is off towards the sampling port and open towards the patient and then flush. Place new sterile cap over sampling port.
Appendix L

*Intra and Inter-Assay Precisions for S100b, IL-6 and TNF-α*

The tables below demonstrate the coefficient of variation (CV%) for S100b, IL-6 and TNF-α. This is calculated for both intra- and inter-assay precision using the following formula:

\[ CV\% = \frac{\text{Standard deviation (SD)}}{\text{Mean}}(100) \]

A figure of 10% or less is considered satisfactory.

**Intra-assay precision for S100b**

<table>
<thead>
<tr>
<th></th>
<th>Level 1 (0.11µg/L)</th>
<th>Level 2 (2.6µg/L)</th>
<th>Level 3 (18.4µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>CV%</td>
<td>6.4</td>
<td>3.9</td>
<td>3.6</td>
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</table>

**Inter-assay precision for S100b**

<table>
<thead>
<tr>
<th></th>
<th>Level 1 (0.11µg/L)</th>
<th>Level 2 (2.6µg/L)</th>
<th>Level 3 (18.4µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>CV%</td>
<td>10.7</td>
<td>2.2</td>
<td>3.2</td>
</tr>
</tbody>
</table>
### Intra-assay precision for TNF-α

<table>
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<th></th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Mean (pg/ml)</td>
<td>2.6</td>
<td>7.2</td>
<td>14.0</td>
</tr>
<tr>
<td>SD</td>
<td>0.23</td>
<td>0.43</td>
<td>0.74</td>
</tr>
<tr>
<td>CV%</td>
<td>8.8</td>
<td>5.9</td>
<td>5.3</td>
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</table>

### Inter-assay precision for TNF-α

<table>
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<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Mean (pg/ml)</td>
<td>2.4</td>
<td>6.7</td>
<td>13.5</td>
</tr>
<tr>
<td>SD</td>
<td>0.41</td>
<td>0.85</td>
<td>1.46</td>
</tr>
<tr>
<td>CV%</td>
<td>16.7</td>
<td>12.6</td>
<td>10.8</td>
</tr>
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</table>
### Intra-assay precision for IL-6

<table>
<thead>
<tr>
<th></th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Mean (pg/mL)</td>
<td>0.44</td>
<td>2.45</td>
<td>5.53</td>
</tr>
<tr>
<td>SD</td>
<td>0.03</td>
<td>0.19</td>
<td>0.41</td>
</tr>
<tr>
<td>CV%</td>
<td>6.9</td>
<td>7.8</td>
<td>7.4</td>
</tr>
</tbody>
</table>

### Inter-assay precision for IL-6

<table>
<thead>
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<th></th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>36</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Mean (pg/mL)</td>
<td>0.49</td>
<td>2.78</td>
<td>5.65</td>
</tr>
<tr>
<td>SD</td>
<td>0.047</td>
<td>0.20</td>
<td>0.37</td>
</tr>
<tr>
<td>CV%</td>
<td>9.6</td>
<td>7.2</td>
<td>6.5</td>
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</table>
# Appendix M

## Mechanism of Injury and Injuries Sustained by Patients Recruited to Observational Study

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Mechanism of Injury</th>
<th>CTB Findings</th>
<th>Other Injuries Sustained</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fell 30 feet from a bridge</td>
<td>Multiple bilateral occipital contusions Left temporal lobe contusions Traumatic subarachnoid haemorrhage Bilateral occipital and parietal fractures Right maxillary sinus haematoma</td>
<td>Bruising and abrasion to right lower leg</td>
</tr>
<tr>
<td>2</td>
<td>Fall down three steps</td>
<td>Thin left frontal Acute Subdural haematoma Bifrontal haemorrhagic contusions Left hemispheric oedema Traumatic subarachnoid haemorrhage Right occipital fracture</td>
<td>Stellate occipital laceration</td>
</tr>
<tr>
<td>3</td>
<td>Assaulted with planks of wood to head</td>
<td>Bifrontal haemorrhagic contusions Bifrontal thin subdural haematomas Interhemispheric haematoma Sphenoid sinus haematoma Left maxillary sinus haematoma</td>
<td>Left mandibular fracture Marked facial swelling Bilateral periorbital haematomas Sublingual haematoma Multiple forehead abrasions</td>
</tr>
<tr>
<td>4</td>
<td>Fall from a first floor balcony</td>
<td>Left occipital contusions Thin right temporal subdural haematoma Pneumocephalus Bilateral occipital fractures Right petrous-temporal fractures Base of skull fracture</td>
<td>T11-T12 spinous process fractures Right L2 laminar fracture Right L3 laminar and spinous process fracture L4 anterior vertebral body fracture</td>
</tr>
<tr>
<td>5</td>
<td>Thrown from motorcycle at high speed</td>
<td>Mild generalised oedema</td>
<td>C7 spinous process fracture Right 4th and 5th metacarpal fractures Right shoulder and wrist abrasions</td>
</tr>
<tr>
<td>6</td>
<td>Cyclist hit by a car</td>
<td>Bilateral basal ganglia contusions</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Driver of a car that hit a wall at high speed</td>
<td>Thin right frontal subdural haematoma Left frontal contusion Left petrous fracture extending into the mastoid air cells Pneumocephalus</td>
<td>Left forehead laceration Left ear laceration Right forearm compartment syndrome</td>
</tr>
<tr>
<td>8</td>
<td>Driver of a car that hit a wall at high speed</td>
<td>Haemorrhagic contusion left cerebellum</td>
<td>Left temporal laceration Right lower chest wall bruising</td>
</tr>
</tbody>
</table>
Appendix N

Temporal Course of ICP and $T_{\text{brain}}$ for Individual Study Patients

Patient 1

Fig. N1 Change in ICP and $T_{\text{brain}}$ during the entire study period.

Patient 1 had a fluctuant ICP throughout the study period. Two episodes of cooling were delivered early following injury and ICP changes during this period are discussed in more detail (3.2.6). ICP became increasingly difficult to control at approximately 40 hours from injury and one of the sedating agents was temporarily increased at 45 hours from injury to assist ICP reduction. Although there were other spikes of ICP >25mmHg, no interventions were required until ICP became increasingly difficult to control at 105 hours from injury. As a result, a thiopentone infusion was commenced 106 hours from injury. This coincided with a rising $T_{\text{brain}}$ and in order to counteract this rise, level 2 cooling was commenced at 108 hours from injury.
Patient 2

Fig. N2. Changes in ICP and $T_{\text{brain}}$ during the entire study period

This patient also had a fluctuant ICP throughout the course of the study period. Two episodes of cooling were delivered early in the patient’s admission and the ICP changes during this time are discussed in more detail (3.2.6). There were a few spikes in ICP not requiring intervention until approximately 68 hours from injury when ICP became more difficult to control. This coincided with raised $T_{\text{brain}}$ and a delivered but not studied level 4 cooling episode. A level 2 cooling episode had already been completed as per protocol and level 4 cooling commenced due to a lack of temperature reduction. As a result of persistent difficulty controlling ICP a thiopentone infusion was commenced at 71.5 hours from injury. Despite maximal medical management ICP continued to be difficult to control. This was exacerbated by respiratory deterioration secondary to a proven chest infection. At 70.5 hours from injury the patient’s oxygen requirements began to increase. Between 82.1 and 101.5 hours from injury and also between 116.5 hours from injury until the end of the study period the patient required between 90 to 100% inspired oxygen. During these periods oxygen
saturations were maintained only in the high 80’s and low 90’s. By the end of the study period ICP remained fluctuant despite continued maximal medical therapy. The patient also required high doses of noradrenaline to maintain CPP.

**Patient 3**

![Graph showing changes in ICP and T<sub>brain</sub>](image)

**Fig. N3.** Changes in ICP and T<sub>brain</sub> during the study period

ICP was difficult to control from early following injury and a thiopentone infusion was commenced at 17 hours following injury. Initially ICP stabilised but from approximately 30 hours from injury continued to rise, despite maximal medical therapy. Prior to a decompressive craniectomy, performed at 52 hours following injury, ICP had risen to a maximum of 46mmHg. This rise in ICP coincided with a steady decrease in T<sub>brain</sub> to hypothermic levels, in the absence of cooling. Despite surgery and continued maximal medical therapy ICP continued to be difficult to control, although T<sub>brain</sub> had risen to normothermic levels immediately post-surgery. Thiopentone was discontinued between 93 and 103 hours from injury and during this period ICP fluctuated between 26 and 49mmHg. During these hours the patient was not receiving any sedation as the sedating agents had been
stopped at 30 hours from injury, due to complete burst suppression. Thiopentone was recommenced between 104 and 111 hours from injury. Despite this ICP continued to spiral and thiopentone was withdrawn. The patient died 121 hours following injury.

**Patient 4**

![Figure N4. Changes in ICP and T_{brain} during study period](image)

ICP was elevated from the time of admission and thiopentone was infused between 14-17 hours following injury. This improved ICP and although at times it was fluctuant, no further intervention for ICP control was required until 70 hours from injury. Indeed, at 33 hours from injury the rate of infusion of two sedating agents was reduced. At 69 hours from injury the sedating agents that had previously been reduced were increased and at 70 hours from injury a thiopentone infusion was recommenced. These measures were required due to sustained rises in ICP. Thiopentone was continued for 11 hours then stopped. At 88 hours from injury there was a further rise in ICP that coincided with an elevated T_{brain} and level 2 cooling and thiopentone was recommenced. Despite this and attempts to reduce T_{brain}, ICP continued to rise. As a result, the patient was transferred to theatre for emergency surgery in
the form of a decompressive craniectomy. Post-operatively ICP was more stable and thiopentone was stopped shortly following surgery.

**Patient 5**

![Graph showing changes in ICP and $T_{\text{brain}}$ during the study period](image)

ICP on admission was high but settled spontaneously and rapidly. Sedation was switched off transiently at 25 hours but recommenced rapidly due to a rapid rise in ICP. ICP generally remained $<$25mmHg and no interventions to reduce ICP were required. Sedation was again switched off at 53 hours from injury but was re-started 12 hours later due to persistent low GCS and a rise in $T_{\text{brain}}$. While sedated there was a further spike of ICP during an episode of level 4 cooling, which is discussed in more detail later. Sedation was finally switched off at 98 hours from injury. Following this there were some transient ICP elevations that may have been related to waking up from sedation and did not require any intervention.
Patient 6

Fig. N6. Changes in ICP and $T_{\text{brain}}$ during entire study period

No cooling episodes were studied in this patient. During the study period there were a few transient spikes in ICP to $>25$mmHg, but no interventions to reduce ICP were required.

Sedation was switched off at 32 hours and recommenced for three hours for a procedure at 55 hours from injury. The ICP probe was removed at 107 hours following injury.
**Patient 7**

![Graph showing ICP and T\textsubscript{brain} for Patient 7](image)

Fig. N7. Change in ICP and T\textsubscript{brain} during study period. Apart from one spike in ICP to 35mmHg early following injury (24 hours), ICP remained stable and below 25mmHg. Sedation was switched off at 55 hours. The ICP probe was removed at 86 hours from injury.

**Patient 8**

![Graph showing ICP and T\textsubscript{brain} for Patient 8](image)

Fig. N8. Changes in ICP and T\textsubscript{brain} during study period
Patient 8 was admitted to ICU 6.6 hours from injury and ICP was difficult to control from an early stage. Despite sedation with propofol, alfentanil and midazolam, a thiopentone infusion was commenced 12.5 hours from injury. The rate of thiopentone infusion was increased 21.5 hours from injury and finally switched off 39.5 hours following injury. The midazolam infusion was stopped a few hours earlier at 36 hours from injury. During the remainder of the study period ICP remained fluctuant but generally <25mmHg and no further intervention was required.
Appendix O

Temporal Course of CPP and Noradrenaline requirements for Individual Study Patients

Patient 1

![Graph showing changes in CPP and noradrenaline requirements](image)

Fig. O1 Changes in CPP and noradrenaline requirements during the entire study period

To maintain CPP > 60mmHg, noradrenaline was commenced 12.5 hours following injury. This coincided with a raised $T_{\text{brain}}$ and a studied episode of level 2 cooling, and the need for increased sedating agents. It was stopped at 18 hours following injury but re-commenced at 37 hours following injury due to difficulty maintaining CPP. Increasing doses were required from approximately 47 hours from injury, in keeping with the need for a temporary increase in one of the sedating agents. Once the sedating agent had returned to its original rate the noradrenaline infusion was reduced but required throughout the remainder of the study period to maintain CPP.
Fig. O2 Changes in CPP and noradrenaline requirements during the entire study period

A low dose infusion of noradrenaline was commenced at 41.5 hours and then stopped at 69.5 hours following injury, although CPP was generally maintained >60mmHg just prior to the start of the infusion. There had been some minor but sustained falls in CPP to just below 60mmHg around 35 hours from injury. At 77.5 hours noradrenaline was recommenced due to a persistent fall in CPP. At this stage the patient required a thiopentone infusion for ICP problems. Also a proven chest infection was causing worsening oxygen saturations and increased difficulty ventilating the patient. Increasing doses of noradrenaline were required throughout the remainder of the study period, as both the chest infection and ICP became increasingly difficult to manage. The patient died 168 hours from injury.
From the time of admission the patient experienced a high ICP and low MAP, resulting in the need for noradrenaline to boost CPP from an early stage (13 hours from injury). ICP became difficult to control again at approximately 30 hours from injury resulting in a downward trend in CPP. Stabilisation of CPP prior to the decompressive craniectomy coincided with the cessation of the sedating agents. These were stopped as the patient was fully burst suppressed with a thiopentone infusion. Following a decompressive craniectomy and despite increasing doses of noradrenaline, CPP followed a downward trend. At 93 hours from injury dobutamine was added. Towards the end of the study period ICP began to spiral, despite maximal medical therapy, and CPP fell dramatically. The patient died one hour following the completion of the study.
Due to a high ICP on admission a noradrenaline was infusion was required from this time. Although there were some fluctuations in CPP following the initial stabilising period, CPP was generally well maintained with a low dose noradrenaline infusion until approximately 80 hours from injury. ICP began to become more difficult to control from about 70 hours from injury and prior to an emergency decompressive craniectomy, noradrenaline requirements were on the rise. Following surgery a low MAP resulted in increased noradrenaline requirements. As the underlying problem was corrected, with increased fluids, the noradrenaline infusion was reduced.
Fig. O5. Changes in CPP and noradrenaline requirements throughout the entire study period

CPP fell to below 60mmHg shortly following admission due to a high ICP (that settled rapidly and spontaneously). A low dose of noradrenaline generally maintained CPP around target values until 53 hours from injury. At this stage sedation and noradrenaline were switched off and CPP rose massively above 60mmHg. Sedation was recommenced 12 hours later and, as a result of a fall in CPP, noradrenaline was also recommenced. CPP remained somewhat fluctuant but generally >60mmHg until noradrenaline was finally switched off at 100 hours from injury, two hours following cessation of sedation. Sedation remained off for the remainder of the study and no further noradrenaline was required to maintain CPP.
Fig O6. Changes in CPP and noradrenaline requirements during the entire study period

CPP was maintained with the assistance of noradrenaline from admission, 12 hours following injury. Noradrenaline was continued until 36 hours from injury, four hours after the cessation of sedation. Up to this point CPP was generally maintained between 50 and 80mmHg. Sedation was re-commenced between 55 and 59 hours for a percutaneous tracheostomy. This was associated with a fall in MAP and a transient rise in ICP, leading to a fall in CPP. Noradrenaline was therefore recommenced and continued until 61 hours from injury. During the remainder of the study period sedation remained off and no further interventions were required to maintain CPP.
Fig.07. Changes in CPP and noradrenaline requirements during the entire study period

Noradrenaline was required from admission, 8 hours following injury. There was a fall in CPP between 18 and 20 hours, as a result of a fall in MAP and also a slight rise in ICP to the low 20’s. This resulted in an increased noradrenaline infusion from 18 hours followed by a reduction titrated to CPP. Prior to cessation of sedation (55 hours from injury) there was again a slight fall in CPP, due to a low MAP, which resulted in a short increase in the noradrenaline infusion. The noradrenaline infusion was stopped 56 hours from injury. No interventions were required to maintain CPP for the remainder of the study period.
Fig. O8. Changes in CPP and noradrenaline requirements during the entire study period

Noradrenaline was commenced 12.5 hours following injury. At this point an additional sedating agent was added and a thiopentone infusion commenced due to a high ICP resulting in a reduced CPP. Throughout the remainder of the study period noradrenaline was continued and CPP was generally maintained above target level. However, at times CPP was much higher than the recommended target level, reaching a maximum of 110mmHg.