Near Infrared Spectroscopy Monitoring in Prehospital Traumatic Brain Injury Care

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Abstract

Traumatic brain injury (TBI) is a significant cause of morbidity and mortality across all age groups. The impact of these injuries can be lifelong and affect not just the individual but those around them and society itself. This has made therapeutic interventions for TBI an area of major interest for researchers and clinicians over decades with minimal change in patient outcomes.

This thesis focuses attention on the moments after the injury. Prehospital medicine is delivered in a challenging clinical environment which makes assessment difficult and provides fewer options for treatment. There is a monitor that is missing from prehospital care - a non-invasive monitor to guide therapy by providing information about the brain itself. This could then guide advanced therapies that can be delivered at the roadside including anaesthesia, intubation and ventilation, blood product transfusion and administration of vasoactive agents.

The physics of near-infrared spectroscopy (NIRS) has been applied to create a monitor that may provide this breakthrough. With optodes placed on the skin, measurements relating to local tissue oxygen saturation and blood volume can be derived with a high degree of temporal resolution. Although the role of NIRS has been explored in a variety of contexts including TBI and surgery its precise clinical role is still being sought.

This thesis explores the potential role of NIRS tissue oximetry in prehospital TBI care. Technical feasibility is established in the context of a pilot study confirming that monitoring data can be obtained in real world conditions. Data collection reached a benchmark of > 70% of total prehospital time delivering successful monitoring capture without evidence of any compromise in patient care.

The thesis then presents different approaches to analysis of NIRS-derived cerebral oximetry. In a study population of trauma patients cared for by an advanced prehospital medical team there was no significant association between cerebral NIRS regional tissue oxygen saturation (rSO_2) < 45% for $\geq$ 1 minute duration and patient outcomes including functional status at 12 months and patient mortality.

There is then exploration of novel analyses utilising machine learning and deep learning to assess whether alternate approaches may allow pattern recognition beyond the discernment of the unaided clinician from both rSO_2 and haemoglobin index (HbI), a measure of blood volume in the sampled area. This analysis did not find any association between NIRS oximetry data and outcomes including patient mortality at 30 days, reduced GCS or significant head injury as shown by AIS (head and neck) $\geq$ 3 when applying statistical analysis or machine learning. However a deep learning approach involving the application of a convolutional neural network (CNN) demonstrated some predictive ability utilising the same data set. This raises the possibility that novel analytic approaches may help define which measurements are clinically meaningful and assist practitioners by prompting interventions. Further development of this approach is critically reliant on further post-processing work to ensure the associations retain direct linkage with patient physiology along with far larger datasets to facilitate model training.

This work explores the potential use of a non-invasive monitor of cerebral tissue to enhance prehospital care of TBI. The monitor demonstrated technical feasibility, however standard analytic approaches did not find meaningful associations between rSO_2 values and either short-term and long-term outcomes or pathology. This may be a result of a requirement for much larger studies to establish adequate power along with significant gaps in the monitoring data. Our further

exploratory analysis suggests that deep learning approaches may be able to discern significant patterns within NIRS oximetry data. Further development of this approach requires engineering improvements to monitors, larger datasets and clearer evidence of the best use of clinically linked monitoring data from the hospital environment to justify further research at the accident scene.

Ethical Clearance

The research described in this thesis was reviewed by, and received peak body ethical clearance from, The Sydney Children's Hospitals Research Network Human Research Ethics Committee (reference number 11/SCHN/212).

Approval to facilitate access to study data at each receiving hospital was undertaken via the local Research Governance process at each of the eight facilities.

Acknowledgements

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This research arose from my involvement with CareFlight, a place for extraordinary people given the tremendous privilege to reach out to patients and good souls in the community in suddenly catastrophic times. Thank you to those we met as patients and every first responder who helped a person in need while awaiting the cavalry – you are at the heart of this research.

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Index of Tables and Figures

Tables

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Abbreviations

$AVDO_2$	Arteriovenous Oxygen Content Difference
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
$CMRO_2$	Cerebral Metabolic Rate of Oxygen
CNN	Convolutional Neural Network
CO_2	Carbon Dioxide
CPP	Cerebral Perfusion Pressure
CRRH	CareFlight Rapid Response Helicopter
CSF	Cerebrospinal Fluid
CW	Continuous Wave
CT	Computerised Tomography
DAI	Diffuse Axonal Injury
DL	Deep Learning
DP	Differential Pathlength
DPF	Differential Pathlength Factor
DRS	Disability Rating Scale
EDH	Extradural Haematoma
FV	Transcranial Doppler Flow Velocity
FVm	Mean Flow Velocity
FVs	Flow Velocity During Cardiac Systole
GCS	Glasgow Coma Scale
GOSE	Extended Glasgow Outcome Scale
Hb	Haemoglobin

HbD	Deoxyhaemoglobin
HbT	Total Haemoglobin Index
HRQOL	Health-Related Quality of Life
IABP	Intra-arterial Blood Pressure
ICH	Intracerebral Haemorrhage
ICP	Intracranial Pressure
ISF	Interstitial Fluid
ML	Machine Learning
Mx	Correlation coefficient index between FVm and CPP
NIRS	Near Infrared Spectroscopy
NPV	Negative Predictive Value
$P_{bt}O_2$	Direct Cerebral Tissue Oximetry
PET	Positron Emission Tomography
PPV	Positive Predictive Value
PRx	Pressure Reactivity Index
PTC	Paediatric Trauma Centre
QALY	Quality-Adjusted Life Year
QOL	Quality of Life
RTC	Road Traffic Collisions
SAH	Subarachnoid Haemorrhage
SDH	Subdural Haematoma
SF-36	36-item Short-Form Health Survey
SjO_2	Jugular Venous Oxygen Saturation
SRS	Spatially Resolved Spectroscopy

Sx	Correlation coefficient index between FVs and CPP.
TBI	Traumatic Brain Injury
THx	Index of THb to ABP
TOx	Index of StO_2 to ABP.
TRS	Time-Resolved Spectroscopy
XAI	Explainable Artificial Intelligence

Publications and Presentations

Peer reviewed journal articles

Chapter 3 of this thesis is published as:

***Weatherall A**, Garner A, Lovell N, Redmond S, Lee A, Skowno J, Egan J.* Study protocol for the PHANTOM study: prehospital assessment of noninvasive tissue oximetry monitoring. Scand J Trauma Resusc Emerg Med. 2014;22:57.

I conceptualized the research proposal, developed the study protocol and undertook the initial drafting of the protocol and manuscript.

Chapter 4 of this thesis is published as:

***Weatherall A**, Poynter E, Garner A, Lee A.* Near-infrared spectroscopy monitoring in a pre-hospital trauma patient cohort: An analysis of successful signal collection. Acta Anaesthesiol Scand. 2020;64:117-23.

I conceptualized the study and designed all study procedures as well as undertaking data collection, participating in data preparation and analysis and preparing the draft of the manuscript along with the senior author.

Papers Submitted for Peer Review

Chapter 5 of this thesis has been submitted for peer review to Acta Anaesthesiologica Scandinavica as:

***Weatherall AD**, Garner A, Poynter E, Skowno J, Egan J, Lee A*

Association between prehospital cerebral oximetry measured by near-infrared spectroscopy and patient outcomes: a pilot study

I conceptualized the study, undertook data collection, participated in data preparation and review and drafted the manuscript.

Chapter 6 of this thesis has been submitted for peer review to Acta Anaesthesiologica Scandinavica as:

***Weatherall AD,** Argha A, Poynter E, Garner A, Skowno J, Egan J, Lovell NH.* Three Approaches to Analysis of Prehospital Noninvasive Cerebral Oximetry Measurements: Statistics, Machine Learning and Deep Learning Methods

I conceptualized the study, undertook data collection and preparation and drafted the manuscript.

Related Presentations

1. HDR Conference, The University of Sydney, 2019. Invited plenary speaker - "Is monitoring the brain at an accident scene even possible?"
2. HDR Conference, The University of Sydney, 2018. "Is monitoring the brain at an accident scene even possible?"

   Awarded Annual Prize for Outstanding Presentation.
3. NIRStralia, Sydney, Australia, 2018. "A window? NIRS and Prehospital Trauma."
4. HDR Conference, The University of Sydney, 2017. "Does new monitoring at an accident impede patient care?"
5. HDR Conference, The University of Sydney, 2016. "Prehospital Assessment of Noninvasive Tissue Oximetry Monitoring."
6. International Conference of Emergency Medicine, Dublin, Ireland, 2012. Invited Speaker - "Prehospital Assessment of Noninvasive Tissue Oximetry Monitoring."

Additional Publications and Presentations

The candidate was a lead or contributing author on the following publications related to tissue oximetry monitoring, traumatic brain injury or prehospital medicine during the period of candidature.

Garner A, Poynter E, Parsell R, **Weatherall A**, Morgan M, Lee A. Association between three prehospital thoracic decompression techniques by physicians and complications: a retrospective, multicentre study in adults. Eur J Trauma Emerg Surg. 2023;49:571-81.

Garner AA, Bennett N, **Weatherall A**, Lee A. Success and complications by team composition for prehospital paediatric intubation: a systematic review and meta-analysis. Crit Care. 2020;24:149.

Garner AA, Bennett N, **Weatherall A**, Lee A. Physician-staffed helicopter emergency medical services augment ground ambulance paediatric airway management in urban areas: a retrospective cohort study. Emerg Med J. 2019;36:678-683.

Weatherall A, Gill M, Milligan J, Tetlow C, Harris C, Garner A, Lee A. Comparison of portable blood-warming devices under simulated pre-hospital conditions: a randomised in-vitro blood circuit study. Anaesthesia. 2019;74:1026-32.

Hanley P, Holden J, Johnson T, Garner A, **Weatherall A**. Two cases of penetrating left ventricular cardiac trauma: Pre-hospital ultrasound and direct to theatre. Trauma Case Rep. 2019;21:100189.

Milligan J, Lee A, Gill M, **Weatherall A**, Tetlow C, Garner AA. Performance comparison of improvised prehospital blood warming techniques and a commercial blood warmer. Injury. 2016;47:1824-7.

Garner AA, Barker CL, **Weatherall AD.** Retrospective evaluation of prehospital triage, presentation, interventions and outcome in paediatric drowning managed by a physician-staffed helicopter emergency medical service. Scand J Trauma Res Emerg Med. 2015;23:92.

Garner AA, Mann KP, Poynter E, **Weatherall A**, Dashey S, Puntis M, Gebski V. Prehospital response model and time to CT scan in blunt trauma patients: an exploratory analysis of data from the head injury retrieval trial. Scand J Trauma Resusc Emerg Med. 2015;23:28.

Barker CL, **Weatherall AD**. Prehospital paediatric emergencies treated by an Australian helicopter emergency medical service. Eur J Emerg Med. 2014;21:130-5.

Garner AA, Lee A, **Weatherall AD**. Physician staffed helicopter emergency medical service dispatch via centralized control or directly by crew – case identification rates and effect on the Sydney paediatric trauma system. Scand J Trauma Resusc Emerg Med. 2012;20:82.

The candidate also delivered the following related presentations

1. Paediatric Anaesthesia Congress of South Africa, Johannesburg, South Africa, 2019. Invited International Faculty. “The Great Monitoring Debate – Vigileo vs Transoesophageal Echocardiography vs Near infrared spectroscopy”.
2. Australian Society of Anaesthetists National Scientific Congress, Adelaide, Australia, 2018. Invited Speaker - “Cerebral Oximetry in Paediatric Anaesthesia”.
3. Society of Paediatric Anaesthesia of New Zealand and Australia Annual Conference, Adelaide, Australia, 2016. Invited Facilitator - “Neonatal Anaesthesia Workshop – Thoracic Anaesthesia and New Monitoring Modalities”

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Chapter 1

Introduction

Seeing Inside the Box

At the moment of an injury, time changes. Forever afterwards there will be a division – the time before and the time after. Where once there was a story being written with some broad arc towards an expected place, there is a blank page and no telling how long the writing of the next page will take or where it will lead.

The shape of what is to come is dependent on the next few minutes or maybe hours. For a critical organ like brain, the first injury is irreversible. It has been and gone and that precise moment of damage cannot be undone. Cerebral tissue, that which governs every part of what we do and who we are, does not have large reserves to draw on for glycolysis when blood flow is compromised or oxygen is not available. For this critical tissue, minutes count.

The first injury has already triggered a cascade of processes that will either create barely a disturbance or potentially bring destruction to vital parts. This secondary injury can be minimised with the right immediate care and intervention. When things go well, instead of a before and after story there will be nothing more than a slight notch as the pen paused on the page.

The focus of much of the literature is what happens when the patient reaches the hospital and PubMed has approximately 1000 times as many articles on hospital care of TBI than prehospital

care. However in Sydney the median time between the accident and arriving at the trauma centre has been shown to be 53 minutes.[1] Maintaining a focus on what happens in the days after the accident without deeply considering this time risks missing a critical period in the evolution of secondary brain injury.

The patient will be met by prehospital clinicians from a variety of backgrounds. This includes paramedics with a range of skills and abilities and physicians from critical care specialties who can bring the intensive care unit to the roadside. All these clinicians are working in an environment that is hostile to the delivery of complex care. Accident scenes force clinicians to provide clinical care in rain and soaring heat and often in an environment of screaming chaos. Traffic, emergency vehicles, hydraulic-driven extrication devices and voices raised to cut through the mess all put themselves in the way of clinical assessment and treatment.

Figure 1: Accident Scene After Patient Extrication. (Image by the Author.)

In such an environment, monitors are critical to begin to understand the picture of patient physiology. A history is often hard to obtain. Observation with the eyes is complicated by variable light. Listening to a chest is a futile endeavour amongst the din of the machines. A monitor that says something about oxygen or blood pressure might be the first bit of solid ground on which to stand as a clinician.

The vital importance of the monitors that are now considered traditional is recognised by their prominence in guidelines for managing traumatic brain injury (TBI) in the prehospital setting.[2] Pulse oximetry, particularly when coupled with a plethysmograph waveform indicating perfusion to an extremity, can reassure the clinician that the patient's airway is patent, the lungs are exchanging oxygen and that blood flow is reaching the tip of the finger. Or it can highlight a life-threatening issue that must be addressed. Blood pressure measurements can provide similar reassurance of haemodynamic stability or flag a critical issue created by hypovolaemia from blood loss or some mechanical problem preventing adequate circulation. Much of prehospital care is focused on rapidly making sure that blood pressure and oxygenation targets are being met to offer the best possible conditions for critical organs.

When it comes to the brain, both peripheral oxygen levels and blood pressure targets act as imprecise surrogates for answering the critical question – is the brain getting what it needs?

Confronted with a patient rendered unconscious by their TBI, a clinician will monitor what they can and try to achieve certain targets. In aiming to make sure that peripheral oxygen saturation is above 90% and that systolic blood pressure does not fall into the hypotensive range we are merely reaching targets that suit the broad mass of the population on the basis of retrospective studies. At the side of the road or in the back of an ambulance what the clinician really wants to know is 'what

is happening inside the skull?'. There is no monitor that lets the paramedic or doctor see inside the box.

A blood pressure measurement taken at the upper arm provides a measurement of general peripheral blood pressure that is representative of what arrives at the Circle of Willis. The peripheral oxygen saturation provides some reassurance that baseline oxygenation has the potential to adequately provide for the metabolic needs of the brain. However whether the blood then flows through the cerebral vessels and oxygen is delivered to the tissues remains unknown.

It is possible that intracranial pressure is elevated and this is impeding blood flow and diffusion of oxygen to the tissues. It is possible that an area of haematoma is directly compromising brain tissue. It is possible that areas of the brain are already so compromised they are unable to extract oxygen, or that the delivery of oxygen to the cells is slow enough that cerebral tissue is hypoxic. Cerebrovascular reactivity may be compromised in such a way that the usual autoregulation that ensures consistent delivery of nutrients to the brain is broken. Blood flow may be dependent on the general haemodynamic state, fluctuating as determined by global perfusion as cerebrovascular control is lost. A blood pressure target that is ideal for the general population represents profound hypotension in an individual accustomed to levels higher than the norm. For this patient a 'normal' blood pressure may represent profound hypotension. All these possibilities are plausible when we cannot monitor the actual tissue we care most about – the brain.

There is a clear need to focus on the hour or more before the patient reaches hospital. There is equally a clear need for monitoring that can help the prehospital clinician understand what is happening at the brain level. This has the potential to empower them to make treatment choices to optimise delivery of oxygen and blood flow for that particular patient with their particular

physiology. This is critical if we are to minimise secondary brain injury as quickly as possible for the benefit of patients.

A Candidate for New Monitoring

Near-infrared spectroscopy (NIRS) tissue oximetry monitoring may offer a new option for monitoring that can meet this need. It requires only sensors applied at the skin. It is portable. It derives measures of oxygen saturation and blood volume within a focused area of sampled tissue using assumptions that do not rely on pulsatile flow which is a significant advantage.

However the clinical application of NIRS has been relatively slow in the hospital setting and a full understanding of how best to use this technology is still developing. There are many underlying assumptions in commercially available monitors that may have an influence on real world clinical utility and still more work to be done how to make the step from the displayed metrics to clinical treatment choices that improve patient condition.

This thesis presents some initial steps to address a broad question – is this a monitor that can work in the prehospital environment and reveal hidden physiology that clinicians can act on to make a difference?

Aim and Scope of the Studies

The aim of the work described in this thesis was to explore the feasibility of NIRS cerebral oximetry in the prehospital trauma setting and then undertake initial work to explore associations between

NIRS-derived cerebral oximetry measurements and patient outcomes, particularly in the setting of TBI.

Feasibility of Prehospital Cerebral Oximetry

While NIRS has been incorporated into clinical research and to a limited degree in patient care in hospitals there is minimal available evidence relating to its application in the prehospital setting. The prehospital environment challenges any monitor in a manner not conceived when designing devices for hospital-based practice. To explore the utility of NIRS monitoring in this environment, it is first necessary to establish that use of the device is technically feasible in this clinical setting. In earlier work, we had established that it was possible to obtain NIRS oximetry readings in volunteers while in outdoor environments, during ambulance transport and during helicopter transport.[3] The feasibility of NIRS oximetry in the prehospital setting with real patients has not been established.

The primary objective of this study was to determine the proportion of successful monitoring, defined as more than 70% of the total monitored pre-hospital time. The secondary objective was to seek evidence of possible interference with clinical care by assessing the association between NIRS monitoring and total prehospital time.

The benchmark of 70% of total monitored pre-hospital time was established after review of monitoring performance of the other clinical monitors in use in our prehospital context.

The study was conducted within the context of the operations of the CareFlight Rapid Response Helicopter Service (CRRH). The clinical team is transported by helicopter to accident scenes after

tasking by the central ambulance control room and comprises an advanced level paramedic and critical care physician. This team provides advanced life support, anaesthesia, intubation and ventilation, thoracic decompression, blood transfusion and peripheral haemorrhage control manoeuvres along with relevant surgical interventions either at the scene or during patient transport. Patients are transported to the hospital either by helicopter or road vehicle.

Each patient had a total of 3 NIRS oximetry sensors applied. This comprised one to each side of the forehead and one at the volar surface of the forearm as a peripheral reference. The proportion of total monitoring time for which measurements were successfully obtained were calculated for each individual sensor for each patient. We also compared on scene time and total prehospital time for those patients who had NIRS monitoring applied, those who had a study observer available but were excluded on scene for other reasons, and those who met exclusion criteria but for whom no study observer was available.

Exploring Associations Between Cerebral Oximetry and Patient Outcomes

The second area of evaluation aimed to establish whether NIRS-derived cerebral oximetry in the prehospital setting displayed any association with short-term and long-term patient outcomes.

This element of the pilot study was undertaken within the same clinical context at CRRH. Abnormal NIRS cerebral oximetry was defined as a regional oxygen saturation (rSO_2) $\leq$ 45% for $\geq$ 1 minute. Exposure subgroups evaluated included patients with severe TBI (with first Glasgow Coma Scale score $\leq$ 12 and AIS (Head) $\geq$ 3), severe traumatic injury (ISS > 15) and paediatric patients (age < 16 years). NIRS cerebral oximetry groups were then compared to the primary outcome of Extended Glasgow Coma Score (GOSE) dichotomized as poor recovery and good recovery. Short-term

outcomes including 24-hour and 30-day mortality were also compared between NIRS cerebral oximetry groups.

Testing New Methods of Analysis of Cerebral Oximetry

The third area of exploration of the pilot study data focused on novel analysis approaches to establish associations with patient outcome or significant cerebral pathology. Both rSO_2 and HbI values for cerebral sensors underwent statistical analysis, feature extraction to facilitate machine learning and application of deep learning utilising a convolutional neural network to test for predictive associations between monitoring data and relevant clinical outcomes including 30-day mortality, initial Glasgow Coma Scale (GCS) score $\leq$ 12 and AIS (Head and Neck) $\geq$ 3.

Significance of the Studies

Feasibility of Prehospital Cerebral Oximetry

The primary outcome of this study establishes that NIRS cerebral oximetry is feasible in the prehospital setting with an ability to achieve monitoring performance similar to that of physiological monitors in use as part of standard care. Setting a pragmatic benchmark for capture of monitoring data is critical to understanding the applicability of this technology in the real world setting. Failing to explore the proportion of successful signal capture would create a risk that gaps in derived data are so substantial that no association could possibly be demonstrated. Setting an unrealistically high benchmark for signal capture creates a risk that the technology can never truly be applied in the prehospital clinical context because the study conditions can never be met in the real world. This addresses a key concern for clinicians seeking to apply research findings in prehospital medicine in that the data obtained and analysis done based on that data is reasonably representative of their experienced clinical context.

Exploring Associations Between Cerebral Oximetry and Patient Outcomes

The analysis undertaken represents a form of 'traditional' approach to analysis of rSO_2. A key threshold point corresponding with a significant cerebral desaturation event is used to dichotomise patients into abnormal or normal NIRS oximetry groups and tested against patient outcomes that are significant in the context of TBI – functional outcome at 12 months and patient mortality. This is a critical step in assessing the potential role of monitoring rSO_2 in the prehospital TBI setting. To pursue rSO_2 as a target with currently available technology the clinician needs to be confident that this value is meaningful.

Testing New Methods of Analysis of Cerebral Oximetry

This is an exploratory analysis with a goal of establishing whether a different approach to interrogating NIRS monitoring data may reveal a more clinically relevant path towards utilising this technology in the prehospital context. Existing work with NIRS cerebral oximetry has shown associations between defined cerebral desaturation and outcomes such as stroke or patient mortality. However treatment algorithms aiming to prevent cerebral desaturation have not shown significant benefit. One explanation for this may be that a single point threshold for rSO_2 does not allow adequate targeting of the specific issue leading to the desaturation, or that it does not flag evolving pathology in a way that allows the clinician to intervene promptly. Low rSO_2 may reflect an end state after which intervention is less likely to be effective. Both machine learning and application of a convolutional neural network technique facilitate pattern recognition within the NIRS oximetry data at levels a clinician cannot detect through visual inspection of monitoring information. The value of NIRS cerebral oximetry in clinical care is still being established by approaches that are a step beyond consideration of rSO_2 and HbI, including a variety of correlation indices. It appears likely that novel approaches to analysis of NIRS data are required to unlock the

true clinical potential of this noninvasive monitor. An ability to establish pattern recognition systems that could flag clinically meaningful changes utilising only rSO_2 and HbI and then alert the clinician would represent a major step forwards.

Overview of the Thesis Structure

There are 6 further chapters in this thesis. Chapter 2 provides the background context for the focus on traumatic brain injury (TBI) starting with the magnitude of the problem that these injuries represent for individuals and society with their impact on long-term functional outcomes along with a review of the underlying pathophysiology of TBI. The chapter goes on to cover the present role played by monitoring in the management of TBI before summarising the key physical principles of near-infrared spectroscopy, how the physics is adapted for use in clinical monitoring and what we know from existing research across a variety of settings. The specific challenges in monitoring patients in the prehospital environment are also covered.

Chapter 3 represents the first publication related to this work and is an ideal study protocol for a comprehensive prospective observational study. This methodology frames that of the subsequent pilot study on which later chapters are built. Chapters 4 to 6 comprise the three further publications central to the thesis. Chapter 4 is the published technical feasibility study. Chapter 5 is the submitted work covering associations between cerebral oximetry monitoring and patient outcomes. Chapter 6 is the submitted work constituting an exploratory analysis testing statistical analysis, machine learning approaches and deep learning utilising a convolutional neural network. Chapter 7 discusses these papers, the implications of their results and issues highlighted by this work. It goes on to discuss conclusions and next steps that might arise from this work.

Chapter 2

Background

Traumatic Brain Injury – The Size of the Problem

Costs

The acquisition of a traumatic brain injury (TBI) can be a devastating event that spreads its impact on individuals and societies over decades. TBI is a leading cause of morbidity and long-term disability in developed economies. There are approximately 2500 new cases of moderate or severe TBI in Australia each year, with a review of associated costs for 2008 suggesting the cost per annum was $8.6 billion when the costs not only of direct medical care but also those of lost productivity and ongoing burden of disease are considered[4]. In that review of the economic impact of TBI each individual patient was estimated to cost $2.5 million in the case of moderate TBI, or $4.8 million in the case of severe TBI. Ongoing costs to society are particularly high given the over-representation of patients of 15-24 years of age in this traumatic injury group and Australian mortality rates for patients with severe TBI reported as high as 35.1%[5]. In Australia the most commonly affected demographic group is young males, with transported-related accidents and falls being the most frequent mechanisms[5].

It is vital to appreciate that costs related to TBI are not only high due to the costs related to initial treatment of patients with traumatic injuries[6]. The disabling effects of TBI may persist for many years. This may be due to neurological impairment, complications secondary to the initial injury,

cognitive impairment, impaired lifestyle functioning (e.g. difficulties returning to employment or managing self-care activities or activities of daily living) and impaired social functioning[7,8].

These profound costs to the individual and society have therefore created significant interest in improving the care of those sustaining a TBI with the goal of having every patient return to their prior life if possible.

Outcomes

Despite much effort, outcomes after TBI have changed minimally over the last 20 years. This is despite advances in most elements of clinical care, including the publication of consensus evidence-based guidelines, prehospital resuscitation, operative technology and intensive care management. Outcomes have lagged even though mortality for other forms of severe trauma have improved over the same time period[9] There are additional challenges in interpreting the success or otherwise of treatments that have been trialled as the literature lacks large numbers of studies with adequate study design or sufficient recruitment to establish small or moderate differences in outcome[10].

Patients with severe TBI in developed countries continue to have an all-cause mortality of approximately 30-35%. Even in those patients who survive the initial injury and reach the hospital, 90% of the subsequent deaths are attributable to the initial TBI[5,9]. Follow-up of patients admitted to Australian and New Zealand Intensive Care Units over a 12-month period revealed mortality at 6 and 12 months of 24.4% (138 of 566) and 26.9% (139 of 517) of all patients[5]. Corresponding figures for those admitted with severe TBI (defined as patients with initial GCS of 3-8) were 31.6% (105 of 332) and 35.1% (105 of 299).

Assessment of these patients at 6 and 12 months utilising extended Glasgow Outcome Score (GOSE) revealed favourable outcomes in 54.9% (311 of 566) and 58.8% (304 of 517) in the all patients analysis. Corresponding figures for those with severe TBI were 44.9% (149 of 332) and 48.5% (145 of 299). Noting that a favourable outcome utilising GOSE includes patients who do not return to their prior level of function or independence, a large proportion of patients who survive carry the impact of their TBI with them through the rest of their life.

These results are similar to previous similar studies conducted in Europe, the USA and Australia published up to 13 years prior to this 2008 study[11–13]. While there are some demographic differences apparent in these studies, outcome measures themselves were not significantly different.

These figures provide high level insights into functional measures of outcome after TBI. However they do not comprehensively describe the range of life impacts experienced by patients. To fully consider outcomes in TBI, it is necessary to consider the impact on quality of life in more detail.

Understanding Quality of Life

Quality of Life (QOL) must be defined in a number of different ways as the particular context in which the judgment is made will influence perceptions[14]. Those who study QOL in the context of life satisfaction and affect describe QOL as being equivalent to subjective wellbeing. This definition holds that QOL can be described as the cognitive and emotional responses to a balance of achievements and expectations.

Health-related QOL (HRQOL) may be considered as a more quantitative approach to QOL measurement. In this context physical, mental and social domains are measured by a quantitative scale. This second definition of QOL is then one where the share of those characteristics felt to be essential to a "good life" can be determined objectively.

Applying theories from economic and management decision-making gives rise to a third use of the term QOL. It incorporates a relatively simple calculation of costs as well as the more difficult challenge of quantifying outcomes. The developed methodology for this second step amongst economists and social researchers involves panels of raters of varying backgrounds reviewing vignettes that demonstrate differences in particular dimensions (such as mobility, symptoms or mental health issues). Panellists then rate the desirability of those specific situations. This assessment of QOL will be influenced both by the life experiences of those involved in the judging process and the context of the society in which the assessment takes place. While fixed points of time are the focus of these assessment, estimating the amount of time an individual will remain within the classified health status assessment allows calculation of quality-adjusted life years (QALYs). In considering the impact of traumatic brain injury on long-term health outcomes, some measure of quality of life is a vital dimension to measure. All these dimensions must be considered when appreciating the full impact of TBI on survivors.

Quality of Life and TBI

The long term social, emotional and cognitive problems experienced by those with TBI are interdependent. These patients' long-term health status is influenced by three principal factors[15]:

1. Neurological mechanisms where the injury causes direct damage to neural tissue involved in the regulation of social and emotional behaviour;

2. Personal attitude towards disability, particularly the level of awareness of any disability secondary to the injury.
3. Social consequences of the functional impairment resultant from the injury.

Generic and widely used QOL assessment tools, such as the Medical Outcomes Study 36-item short-form health survey (SF-36) may be used in this setting.[16] However there are validated scales for measuring QOL after TBI[17]. These include the GOS, GOSE and the Disability Rating Scale (DRS) Scale[18,19]. Important to any assessment is the fact reporting should be by the individual concerned or a close relative or carer[20].

Ongoing neurological impairment that *impacts on physical abilities* is a key element of subsequent QOL. This is particularly true in the early stages after incurring the injury. Repeat assessments show that physical symptoms tend to decrease and psychological and social problems persist, becoming the major reason for impaired QOL[21].

This does not lessen the importance of considering the contribution of the physical dimension to QOL as symptoms can remain part of the picture. This is particularly true for those with severe brain injury. Assessment up to 8 years later found more than 40% of patients suffering from coordination disturbance, speech disorders or cranial nerve lesions, and up to 25% of patients suffering from difficulties in expressive speech[22]. Headache may also continue to be a significant feature for some patients[23].

Persisting *disabilities in cognitive function* including concentration, language, executive facilities and mental speed are commonly reported after TBI, particularly in moderate to severe injuries.[20] Symptoms of cognitive dysfunction may evolve over time. Fatigue tends to decrease over time

while deficits in memory tend to persist and irritability tends to increase over the first two years after the injury.[21] The perception of the most significant dysfunction also varies depending on who is reporting the symptoms. Patients themselves have been shown to report problems of memory or calculation more often than relatives, who focused on the patient's irritability or tendency to display anger.[24]

Psychological issues are prominent after TBI. This is particularly true for anxiety and depression with rates as high as 77% reported[25]. After TBI, the presence of psychological disorders is more predictive than physical dysfunction for return to work. Research examining patients' assessment of psychological factors indicated that a majority felt their personality had changed unfavourably after their injury, a finding confirmed by relatives[24]. Relatives described patients as more dependent, irritable, excitable, lifeless and childish.

A final critical dimension impacting QOL relates *to social functioning*. Assessment of this dimension includes consideration of relationships and interpersonal conduct as well as vocational status. Resumption of work is a useful way of assessing QOL after TBI. In one series following those with moderate to severe head injuries, 33% were employed one year after the injury, with this figure increasing to 46% after two years. However, only one person in the group returned to their pre-injury work[21]. Melamed et al. also demonstrated that only 49% of study subjects were employed up to 2 years after the injury, and 19% were employed under special conditions[26].

Vocational status serves not only as a marker of QOL but is itself crucial to the patient's opinion of their health status. Subjective assessment of rehabilitation success was linked in this same study to the relationship of the post-injury vocational status when compared to that prior to injury. Work

status also influenced the patient's acceptance of their residual impairments. Unsurprisingly, more severe initial injuries are associated with lesser vocational outcomes[21,27,28].

TBI is therefore a significant public health issue. It particularly affects the young and can have lifelong implications relevant to all dimensions of their quality of life. The final picture of altered QOL is, however, the result of multiple types of injury.

Types of Traumatic Brain Injury

TBI is a term covering many pathologies. Some are focal and some are diffuse. There may be mixed pictures. The subtypes are highly relevant to attempts to improve TBI care as there are implications for patient monitoring and treatment, particularly in terms of scope for surgical intervention.

Extradural Haematoma

Extradural haematoma (EDH) particularly affects the superficial areas of the brain. In adults it is found in up to 4% of TBI cases, with the peak incidence in the second decade and the mean age of patients between 20 and 30 years of age[29].

An EDH arises in the potential space between the dura and the skull. Blood vessels or brain parenchyma can get damaged due to acceleration along the diameter of the skull. The bleeding that gives rise to EDH is most often secondary to arterial injury. The most common site of bleeding is parietal, followed by temporal, frontal, temporoparietal and occipital[30].

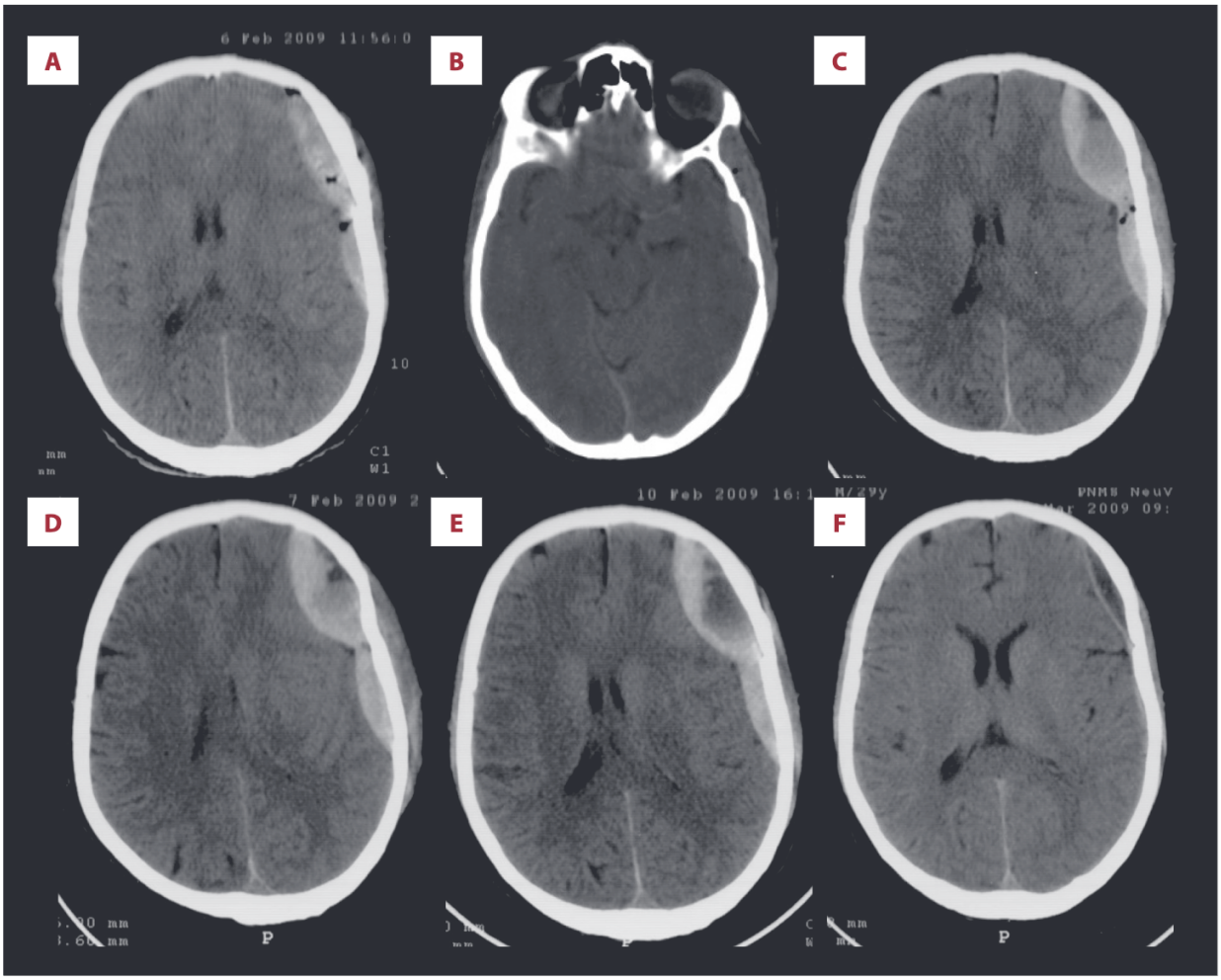

Figure 2: Computerised tomography of head revealing epidural haematoma in left fronto-temporal region underlying a temporal bone fracture. (A) Admission; (B) Temporal skull fracture; (C) After 6 hours; (D) After 24 hours; (E) After 5 days; (F) After 20 days. [Reproduced from Maugeri et al. under Creative Commons Licence CC BY-NC-ND 4.0][31]

Depending on the severity of injury consciousness may be significantly or minimally impaired. EDH is particularly associated with a lucid interval after the injury followed by deterioration, although this is not the only presentation of reduced consciousness. Deterioration is generally secondary to the mass effect created by expansion of the blood in the extradural space and resulting elevated intracranial pressure (ICP). Elevated ICP is more common with severe injuries which are also more likely to be associated with herniation of brain structures. Such herniation is associated with worse outcomes.

Patients with a smaller EDH, representing less than 30 mL of accumulated blood in the adult patient, may be managed without surgery. This is dependent on a favourable location of the EDH

as well as minimal mass effect. Temporal and posterior fossa regions appear to be inappropriate, while CT criteria to satisfy include a thickness of less than 15 mm, a volume of less than 30 mL and a midline shift of less than 5 mm[30].

In those patients who do progress to surgery, the overall mortality across all age groups and GCS scores is approximately 10%.[29] Contributors to the decision of whether to undertake operative intervention include the patient's GCS score, pupillary exam, comorbidities, findings on computerised tomography (CT), age and, where decisions are delayed for initial conservative treatment, the patient's ICP.

Preoperative unconsciousness has a significantly negative effect on mortality and functional outcome for patients with EDH[29]. Associated brain injuries including severe subarachnoid haemorrhage or intraventricular haemorrhage, focal brain contusion of more than 2 cm in diameter or multifocal brain contusion or concomitant large subdural haematoma shows strong associations with worse outcomes after operation. In one series with 200 patients, those with associated injuries had a mortality rate of 14.9% vs 2.3% and unfavourable functional recovery in 35.5% compared to 7.6% for other patients[32].

An additional important factor in patient outcome is the time elapsed between any herniation of brain tissues and surgical intervention. Lee *et al* demonstrated a significant correlation between the duration of brain herniation, as indicated by pupillary changes, and patient outcome.[32] Cohen et al also reported poor outcomes in patients with anisocoria for longer than 70 minutes before surgical intervention.[33] Earlier, Haselsberger *et al* demonstrated that an elapsed time between onset of unconsciousness and surgical evacuation of more than two hours was associated

with an increased mortality of 65% vs 17% and a decrease in favourable outcome of 13% compared to 67%.[34]

The profound influence of time between development of significant clinical changes and surgical evacuation on patient outcome and mortality highlights the potential value of any monitoring that can act as an early warning of imminent changes in patient condition or evolving pathology.

Subdural Haematoma

Subdural haematoma (SDH) is defined by bleeding in the space between the dura and the arachnoid membranes. Rates of SDH are increasing[35]. This is particularly the case for older patients. Although the overall picture for TBI is of minimal change in patient outcomes, for SDH there has been some improvement in discharge disposition and length of hospital stay. In one recent series the overall mortality rate was 14% (200 of 1427 patients) and 94% of patients had only a mild decrease in GCS at discharge (1090 of 1427) while 55% were discharged directly to home[36].

This difference leads to a different appearance on cerebral imaging. SDH typically looks crescent-shaped as it is limited by dural attachments, while being able to cross the margins of sutures in a way EDH cannot.

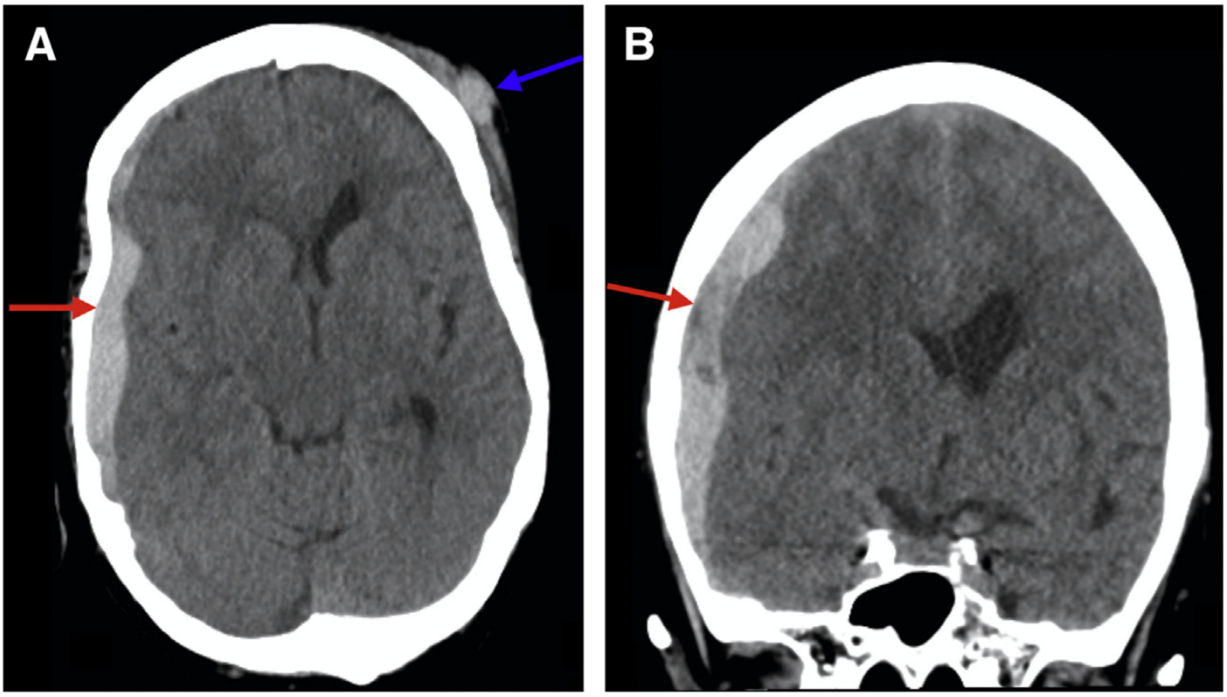

Figure 3:Axial (A) and coronal (b) non-contrast CT of traumatic acute right convexity subdural haematoma (red arrows). The blue arrow highlights a left frontal subgaleal haematoma indicating the contrecoup nature of the subdural haematoma. [Reproduced from Carroll et al with permission.][37]

Arterial rupture, generally related to small arteries related to the cortex that are < 1 mm in diameter, can account for bleeding but is less common than venous bleeding.[38] Venous bleeding is due to tearing of bridging veins that drain to the dural sinuses after arising from the brain surface. Such venous structures may be several mm in diameter. As this venous bleeding is of relatively low pressure, rising intracranial pressure generally stops further bleeding. Otherwise direct compression by associated clot may contribute to arrest of this bleeding.[38]

The difference in involved vessels may lead to some differences in the classic crescent-shaped morphology of the blood collection on cerebral imaging that results from the limits imposed by the attachments of the dura. However the differences in appearance between arterial and venous bleeding are not as distinct as might be assumed. Arterial haematomas are associated with greater maximal and mean haematoma thickness[38]. Arterial SDH also shows a closer association between the degree of midline shift and the haematoma thickness than venous SDH.

Perhaps more significant than these parameters alone is the location of the initial rupture. Rupture sites near the upper longitudinal cerebral fissure have greater scope for spread across the affected hemisphere. When the rupture occurs in the temporal region, a small collection of blood has less scope for spread and may be associated with worse clinical condition.

Improvements in patient outcome should not be assumed to be related to surgical advances as not all patients with SDH require operative management. One retrospective review after the introduction of a policy to prefer non-operative management in patients with SDH measuring < 1 cm thickness on CT scan showed 96% had a good outcome and only 6% of the original 122 patients reviewed required a switch to an operative treatment plan[39]. The overall trend in craniotomy and burr hole procedures for management has generally decreased.[35] Retrospective data derived from reviewing 1427 patients indicated only 248 patients (17%) required surgical evacuation of their haematoma[36]. In this group even the rate of evacuation in patients with a GCS of 5 or less was only 34% (compared to 28% in those with a higher GCS).

Timing of surgery is most influenced by the clinical condition of the patient. Previous retrospective reviews have indicated that patient mortality is lower in patients who experience a longer wait between arrival in the emergency department and craniotomy.[40] However this is explained by the fact that those patients with the most serious injuries are prioritised for rapid intervention and the same study showed a longer prehospital time was associated with worse mortality.[40] Time elapsed between onset of coma and surgical intervention is meaningful, much like in EDH.[34] When the duration extends beyond two hours, mortality has been shown to rise from 47 to 80% with favourable outcome falling from 32% to 4% given the same delay.

Again, early alarms from a patient monitor that could highlight evolving changes could make a difference to timing of intervention.

Traumatic Subarachnoid Haemorrhage

Traumatic subarachnoid haemorrhage (SAH) may be an isolated result from an insult or associated with other TBI. It can be seen across the full spectrum of TBI from mild to severe.
In the setting of mild TBI it is very unlikely to be associated with deterioration and ongoing imaging is therefore unnecessary.[41] Similarly those patients with isolated traumatic SAH are at low risk of clinical deterioration.[42]When compared to other injury types resulting in mild TBI, defined by initial GCS 13-15, in a total cohort of 404 patients, only one with traumatic SAH confirmed by CT deteriorated[42]. The overall rate of progression of haemorrhage on subsequent imaging has been described rates of 1-3.1%**.**[41,43]

It is still possible that SAH may be associated with decreased level of consciousness for a variety of reasons. This includes development of acute hydrocephalus, associated intraparenchymal haematoma or subdural haematoma as well as mechanisms leading to global cerebral ischaemia such as cerebrovascular spasm or associated acutely elevated intracranial pressure.[44] The picture does appear to be distinct from aneurysmal SAH with therapies such as the calcium-channel antagonist nimodipine not showing convincing therapeutic benefit.[45]

The demonstrated low rate of clinical deterioration associated with isolated traumatic SAH is also associated with a low likelihood of requiring surgery. In the studies noted above by Levy *et al* and Quigley *et al*, surgical intervention occurred in 0-0.2% of isolated traumatic SAH patients. If surgery is necessary in a patient with traumatic SAH, it is more likely to be needed due to a separate injury

requiring surgery or intracranial pressure monitoring. Unlike SAH related to aneurysmal bleeding, surgical intervention specifically related to the haemorrhage itself is generally confined to ventricular drainage or intracranial pressure monitoring.

Diffuse Axonal Injury

Diffuse axonal injury (DAI) is associated with widespread damage to axons, diffuse vascular injuries and cerebral oedema[46]. Superimposed on this picture is a degree of hypoxic-ischaemic injury. The formal diagnosis of DAI requires reduced level of consciousness for more than six hours and widespread white matter injuries[46]. Further grading on the basis of lesion depth on cerebral imaging is possible. Grade 1 represents a pattern of lesions confined to lobar white matter at the interface between the grey and white matter. Grade 2 includes lesions in the corpus callosum and grade 3 includes lesions to the brainstem.

DAI is a result of shear and stress of axons during extremes of head movement. Although axons have visco-elastic properties, in TBI the limits of elasticity can be reached and the integrity of axons is disrupted[46]. It appears that lateral head movement results in more severe diffuse damage than movements in the sagittal plane. The nature of injury is also influenced by the severity of the insult. In mild injury only neurofilaments may be damaged. More severe injuries change axonal permeability and there is more widespread disruption of the cytoskeleton[47].

DAI is particularly significant in the trauma profile for patients in road traffic collisions (RTCs). One forensic medicine series describes 80 cases of closed head injury reviewed for underlying pathology in which DAI was present in 25 out of 49 (51%) patients involved in traffic accidents[48].

It is thought that the deceleration of the head is slower than in falls against hard surfaces because of the deformable structures surrounding the head in motor vehicles.

DAI itself is a predictor of poor long-term outcome at 12 months[49]. Management options in DAI are limited surgically. Pressure monitoring may be instituted to help guide perfusion pressure titration. This may be coupled with an external drainage device to allow drainage of cerebrospinal fluid (CSF) to reduce intracranial pressure. Otherwise prevention of secondary injury by avoiding hypoxia or hypotension are the key goals of care.

Other Forms of Injury

The above descriptions do not imply that TBI produces a single pathology in each patient. Any of the above findings may coincide. It is also possible to have intracerebral haemorrhage (ICH) within parenchymal tissue in any location in the brain. Parenchymal ICH is frequently not appropriate for surgical drainage as only up to 30% are solid in appearance with a large proportion having a petechial appearance instead[50] Some intraparenchymal lesions will increase in size and do require drainage. In patients with ICH, it remains the case that the biggest predictor of outcome is the presence of other TBI-related injuries.

Key Features of Cerebral Physiology

An understanding of the role of physiological monitors is only possible if there is some understanding of the underlying physiology.

Cerebral Blood Flow and Autoregulation

The brain normally maintains cerebral blood flow (CBF) at approximately 57 mL/100 g brain tissue/min.[51] However comparisons of CBF in the first 4 hours after injury in patients with TBI showed mean CBF in survivors of 32 mL/100 g/min while non-survivors had a mean flow of 20 mL/100 g/min indicating there is some reserve before significant damage to cerebral tissues occurs.[52]

The maintenance of adequate CBF is achieved through more than one mechanism with the end result being stable delivery of substrates across a range of mean arterial pressures.[53] The three key contributors to this elegant physiological guarantee can be categorised into cerebral autoregulation, neurovascular coupling and vasomotor reactivity for the purposes of description although these mechanisms are very much enmeshed.

The first of these, *cerebral autoregulation*, describes a change in cerebral vascular resistance generated in response to changes in perfusion pressure such that blood flow remains constant. An increase in CPP is met with cerebral vasoconstriction so that the increased pressure does not result in excessive CBF. A reduction in MAP results in vasodilatation to ensure flow is not inappropriately limited.

Initial descriptions of cerebral autoregulation suggested a plateau range of MAP from 50-160 mmHg within which CBF remains constant but this is now thought to be an oversimplification. The increase in vascular resistance with elevated MAP is effective at guaranteeing constant flow. However when MAP decreases, the resultant cerebral vasodilatation is not quite sufficient to maintain a perfectly constant CBF.[54]

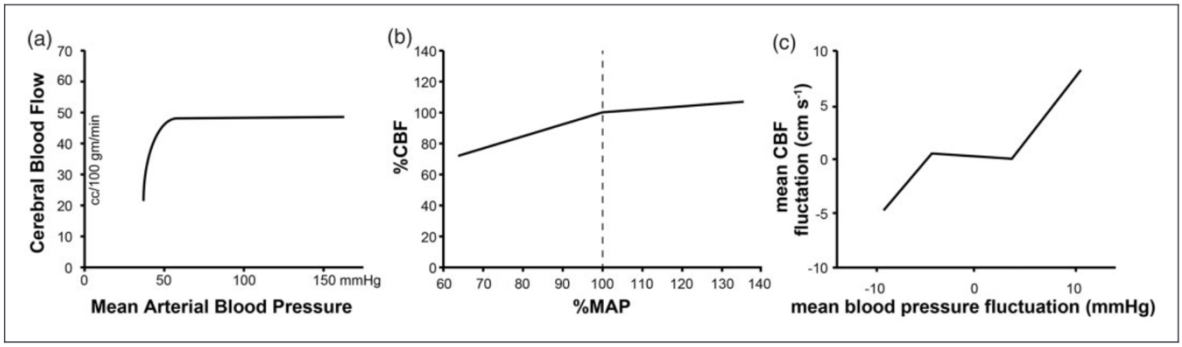

Figure 4: Evolution of the understanding of the relationship between mean arterial pressure (MAP) and CBF. (a) Shows the plateau region with stable CBF across a wide range of MAP. (b) An intra-individual autoregulatory curve indicating that as MAP falls from an ideal starting point cerebral vasodilatation is insufficient to maintain constant CBF. (c) Depicts the dynamic cerebral autoregulation that occurs over seconds as MAP fluctuates. [Reproduced from Slupe et al. with permission.][54]

Across the rest of the body, vascular tone is significantly influenced by the autonomic nervous system. However within the cerebral vasculature it appears that intrinsic mechanisms are more influential than this broader neural control. The mechanisms that generate myogenic tone are generated at the level of the 'neurovascular unit', a functional unit incorporating vascular smooth muscle, endothelium and neighbouring neurons and astrocytes. Vascular smooth muscle appears to generate a resting tone that is significantly determined by mechanosensitive transient receptor potential (TRP) channels. These channels alter the conductance of cations in response to the degree of stretch or shear applied by the perfusion pressure. More stretch or shear leads to more conductance and vasoconstriction. The other participants in the neurovascular unit then modulate this underlying myogenic tone.

TRP channels at the level of the endothelium exert a different influence with smooth muscle relaxation resulting from the generation of nitric oxide. The endothelium is also a source of prostanoids that produce vasodilatation. The other key participants in the neurovascular unit, astrocytes and neurones also produce arachidonic-acid derived products and, in the case of

neurons, nitric oxide to produce a degree of vasodilatation that underpins an established myogenic tone.

The result of all these myogenic influences is a degree of static cerebral autoregulation that dictates a baseline over minutes to hours but with an ability to respond dynamically to changes in pressure over seconds to minutes.

Neurovascular coupling is a term describing regional changes in CBF coupled to the cerebral metabolic rate of oxygen ($CMRO_2$). This metabolic autoregulation occurs at the level of small cerebral vessels and all members of the neurovascular unit are involved in this regulatory mechanism that is responsive to the needs of surrounding cells. Active neurones release nitric oxide which produces dilatation when it diffuses to nearby vascular smooth muscle. Substances such as adenosine, prostaglandins, epoxyeicosatrienoic acid, K^+ and Ca^{2+} are all released from active astrocytes and neurons into the perivascular space. Pre-clinical work suggests that vessels within 1mm of active neurons are, through this mechanism, responsive to changes in neuronal activity within seconds.[55] It should be noted that changes in global parameters such as blood viscosity may also produce conditions that influence the metabolic contributors to autoregulation.[56] With higher viscosity and a slight reduction in CBF, slower flow through smaller vessels creates similar metabolic conditions that result in dilation of small vessels via the metabolic mechanism. The result of these mechanisms is that the arteriovenous oxygen content difference ($AVDO_2$) should remain essentially constant under physiological conditions.

The final significant element to consider with respect to CBF is *vasomotor reactivity*, particularly to arterial CO_2. Cerebral vasoconstriction occurs with low arterial CO_2 levels while vasodilatation is the result of hypercarbia. Alteration of cerebral vascular tone in response to the presence of CO_2

and, to a lesser extent, a deficit of O_2 occurs at both arterioles and larger calibre vessels and is an intrinsic property of the vasculature and this reactivity is independent of adrenergic activity.

The precise mechanism linking CO_2 tension to cerebrovascular state are not clear. Initial indications were that extracellular pH due to diffusion of CO_2 either into or out of the vasculature was the dominant mechanism however more recent work suggests that vascular smooth muscle intracellular pH is also a contributor.[57]

A key difference between vasomotor reactivity and the forms of autoregulation noted above is that whereas those alterations maintain stable oxygen delivery, changes in CO_2 result in primary changes in vessel diameter and a passive change in CBF and $AVDO_2$. The result is that for each 1 mmHg change in p_aCO_2 across a range of 20-80 mmHg there is a roughly linear relationship with CBF which will change 1-6%.[58] The change in $AVDO_2$ is therefore not an adaptive change. This CO_2 reactivity is a key target of therapeutic ventilation to maintain intracranial pressure.

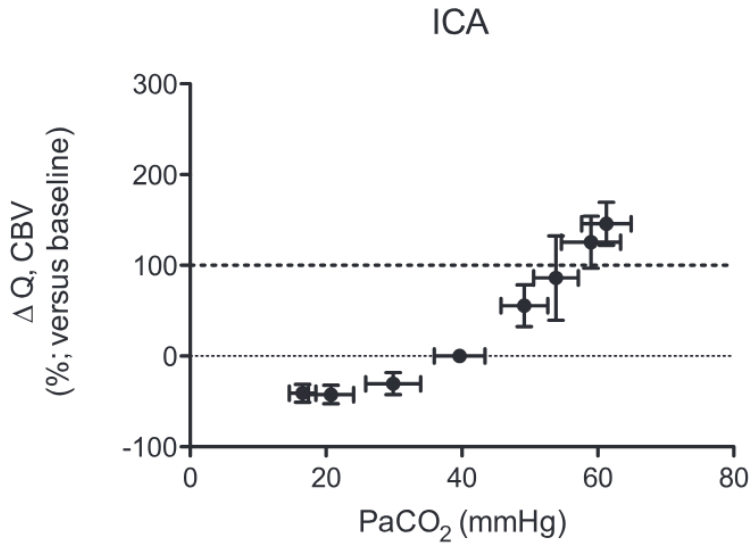

Figure 5: Percentage change in blood flow and cerebral blood volume vs baseline as arterial carbon dioxide increases. [Reproduced from Willie et al. with permission.][58]

Ultimately these autoregulatory mechanisms are critical to maintaining a consistent cerebral perfusion pressure (CPP) to ensure adequate delivery of substrates to the brain tissue. CPP is defined as the difference between the mean arterial pressure (MAP), reflective of systemic blood pressure, and the competing pressure inside the rigid cranium, the intracranial pressure (ICP). It can therefore be expressed as:

$$CPP = MAP - ICP.$$

Intracranial Pressure

Normal ICP is determined by the 3 principal tissues within the rigid vault of the cranium[59]:

1. Cerebral tissue (approximately 83%).
2. Blood volume (approximately 6%).
3. Cerebrospinal fluid (CSF) (approximately 11%).

Normally, ICP is maintained in the adult between 7-15 mmHg. In part this is maintained by adjustments in one of these three “compartments” to accommodate the change in any other parameter. In the setting of raised cerebral tissue volume, some CSF may be mobilized to the spinal space initially. Likewise changes in blood volume can influence ICP. This can be in the form of extrusion of blood, principally the venous component, from the intracranial space. A vasogenic influence on ICP is also in constant operation with vasodilatation in the presence of raised CO_2 or vasoconstriction when CO_2 is decreased.

The definition of raised ICP is somewhat dependent on age and the underlying pathology involved. While ICP > 15 mmHg would generally be considered abnormal, in a setting such as TBI treatment

has traditionally been instituted when ICP exceeds 20 mmHg in an adult but at any value above 15 mmHg in infants or 18 mmHg in children < 8 years of age.[60]

Pathophysiology of Traumatic Brain Injury

Traumatic brain injury may be caused by direct application of forces to tissues, as in penetrating injuries, but is more commonly a result of indirect forces creating motion within the different tissue types within the rigid cranium. The rapid acceleration and deceleration of the structures within the brain results in the generation of both linear and rotational forces.[61] The tissues within the brain are not uniform in their viscoelastic properties and are surrounded by fixed structures with little internal support. Thus, the superficial grey matter is particularly susceptible to linear forces and deeper white matter is more sensitive to rotational forces, inducing DAI.

Following this initial injury, further secondary insults may be induced by hypoxia, systemic hypotension and disturbances in intracranial pressure and cerebrovascular autoregulation beyond normal limits.[62,63] More is being revealed about the role of the blood-brain barrier (BBB), neurons and glial cells in the generation and propagation of brain injury, as well as the role of neuroinflammation and cytokines and other substances.[61] Assisting in this exploration is the fact that similarities in pathophysiologic pathways exist between TBI and other conditions such as intracerebral haemorrhage[64] and subarachnoid haemorrhage[65], allowing insights obtained from the study of other conditions to shed light on processes in TBI. The picture of the elements contributing to the evolving pathophysiology of TBI is therefore a complex one.

Oedema in Traumatic Brain Injury

A critical step in the disruption of normal physiology in TBI is the development of oedema. This had been traditionally considered as primarily created by a vasogenic effect as compromise of the blood brain barrier (BBB) and associated vascular engorgement lead to an increase in cerebral volume. However it is now understood that a cellular or cytotoxic mechanism for oedema is dominant.[66]

The BBB is created anatomically by the tight junctions connecting endothelial cells In cerebral vessels, supported by astrocytes with their foot processes forming an integral part of the anatomical unit. These astrocytes also release chemical factors that regulate properties of the BBB including permeability, endothelial interactions with immune cells and transport activities. In TBI the BBB is disrupted with a resultant increase in permeability of the BBB to both low- and high-molecular weight substances. Factors including reactive oxygen species, proinflammatory cytokines, vascular endothelial growth factor, matrix metalloproteinases and vasopressin and its associated central nervous system receptor V_{1a} are all implicated in the processes that increase BBB permeability.[61,65,67,68] The result is accumulation of osmotically active molecules in cerebral interstitial fluid.

While important in the early development of oedema, animal studies indicate that the initial increase in diffusion of substances across the BBB is followed by a rapid decrease in permeability, even as brain water content increases.[66] Follow-up work in humans has confirmed this picture.[69]

This supports the importance of cytotoxic oedema in the process particularly as raised ICP that is refractory to therapy tends to be a feature days after the initial injury even as the BBB is recovering. Cytotoxic oedema is a result of changes in permeability of cell membranes to Na^+ and K^+, failure of ion pumps such as Na^+/K^+-ATPase with resultant energy depletion and a sustained uptake of osmotically active solutes.[70] The result is accumulation of intracellular water in neurones and glial and endothelial cells.

The implications of cerebral oedema in the context of TBI are profound. It is not necessarily uniform and therefore contributes to a picture of raised ICP and alterations in CBF that are similarly heterogeneous depending on the precise pathological picture.

Cerebral Blood Flow in Traumatic Brain Injury

Cerebral blood flow (CBF) is of particular interest in the setting of TBI, as systemic hypotension (defined as systolic blood pressure < 90 mmHg) has been repeatedly shown to be associated with poor outcomes.[62,71,72] Low cerebral perfusion pressure has been similarly implicated in poor functional outcomes after TBI.[72]

For adequate delivery of substrates, cerebral blood flow must be maintained, even in the setting of raised intracranial pressure. TBI is associated with disruption to the usual processes of autoregulation right down to regional and local tissue levels such that global CBF may not appear to be altered, even as areas of the brain are suffering from ischaemia.[73] Cerebrovascular responses are altered even in mild TBI.[74] Alterations in cerebrovascular reactivity contribute to changes in CBF that put tissues at risk of oedema at the same time as normal ICP responses are impaired.

TBI is therefore associated with disruption to the normal mechanisms that defend cerebral blood flow to ensure tissue oxygenation at precisely the time when cerebral oedema and derangements in intracranial pressure are threatening that delivery. Tissue ischaemia is part of the picture of poor functional outcome after TBI.[53]

Intracranial Pressure in Traumatic Brain Injury

There are many potential causes of raised ICP after TBI. Increased ICP may be related to cerebral oedema, as well as vascular engorgement, intracranial mass lesion and contusion. In the setting of pathology, ICP is not evenly distributed, partly because CSF does not circulate freely. This is particularly important to understand in the context of monitoring as any chosen methodology, whether intraparenchymal or by placement of a catheter in the CSF, is a measurement that may not reflect conditions throughout the cranial space.

Increased ICP eventually critically reduces CPP and CBF and may therefore contribute to the secondary injury. High ICP is strongly associated with poor outcome.[75] While it most commonly develops within 5 days of the traumatic injury, there is some evidence suggesting that around 20% of patients develop their highest mean intracranial pressure after day[76] Those patients developing raised intracranial pressures after day 5 tend to have a higher mean ICP as well and analysis across all 201 patients in this study showed that mean ICP increased until days 12-13. Altered ICP with its potential to interfere with CBF and oxygen delivery is therefore an alteration that threatens brain tissue for weeks.

Other Contributors to Cerebral Injury in TBI

A number of other factors are part of the secondary injury to cerebral tissue. The normal function of mitochondria is significantly disrupted in the context of TBI. Mitochondria are particularly critical for neurons that have minimal ability to undertake anaerobic glycolysis or draw on tissue stores of ATP when substrate delivery is interrupted. These organelles also help maintain intracellular calcium levels at non-toxic levels through their ability to store large amounts of calcium, a process dependent on normal substrate delivery to maintain the negative mitochondrial matrix potential.[77]

In the setting of TBI, disruption to the normal maintenance of intracellular calcium levels result in excessive calcium adsorption to mitochondrial membranes, inhibiting function. In rats, mitochondrial dysfunction begins within 1 hour and persists for at least 14 days.[78] The elevated calcium and oxidative stress contribute to opening of the mitochondrial permeability transition pore. Mitochondria then depolarize, swell and subsequently release cytochrome c into the cytosol, where it becomes part of the apoptosis pathway.

Excessive intracellular calcium levels also activate proteases, lipid peroxidases, and phospholipase with a resultant increase in the intracellular concentration of free fatty acids and free radicals. These are further elements of the contribution of Ca^{2+} ions to a picture of both necrotic and programmed cell death.

Excessive release of the neurotransmitter glutamate has been documented both in laboratory studies and clinical studies after TBI and cerebral ischaemia.[79–81] This is implicated in subsequent neuronal death through apoptosis and related to neuronal swelling. The glutamate in

the synaptic cleft causes repetitive stimulation of glutamate receptors which is then directly linked to excitotoxicity. There is some animal work to suggest that changes in the NMDA receptor subunits are also induced by percussive TBI[82]. These hint at further complex issues with glutamate handling.

TBI is associated with increased brain lactate production. Extracellular fluid glucose declines to extremely low levels as lactate increases. A shift to anaerobic metabolism is also seen, either secondary to hypoxia in the tissues, or in the setting of mitochondrial dysfunction. Generation of lactate appears to occur even in the absence of blood flow limitation, with elevation of lactate occurring in the presence of seemingly adequate cerebral blood flow and with brain oxygen levels within the normal range. After this initial increase in glycolysis, over the next 4 weeks, decreased metabolism of oxygen and glucose is seen, in both animal and human models[83].

Lactic acidosis probably contributes to cell dysfunction and death in its own right, rather than purely being a marker of cell dysfunction. Acidosis promotes cytotoxic oedema, localized particularly to the endfeet of astrocytes. Marked acidosis may also exacerbate the calcium-mediated damage seen in association with high intracellular calcium levels[53].

The pathophysiology of TBI is therefore complex. Biomechanical damage to tissues initiates vasogenic and cytotoxic processes that lead to cerebral oedema, coupled with alterations in CBF and cerebral autoregulation and a significant potential for alterations in ICP. All of these changes are associated with alterations in substrate delivery and utilisation while evolving cellular dysfunction contributes to increased lactic acid production along with necrotic and apoptotic cell death.

Traumatic Brain Injury – A Summary

Traumatic brain injury imposes a devastating burden on both the individual and society with costs each year in Australia amounting to billions of dollars. Improvements in patient outcomes have been minimal despite advances in hospital care. Beyond the tragedy of initial mortality, patients are often left to struggle with profound impacts on their quality of life across all domains – cognitive, physical, psychological and social.

While there are a number of subtypes of TBI, critical damage to cerebral tissue is a result of disruption of the miraculous physiological processes that usually ensure consistent delivery of blood flow and therefore vital substrates for normal metabolism. Direct biomechanical damage is associated with the development of cerebral oedema, alterations in cerebrovascular function and raised intracranial pressure. These contributors to secondary injury are critical to whether patients recover completely or have permanently altered functioning.

Attempts to minimise this secondary injury are therefore critically dependent on understanding what elements are contributing the most to the pathophysiology so that treatments can be initiated to support brain tissue. This understanding is therefore equally dependent on the application of patient monitoring.

Available Monitors to Guide Clinical Intervention in Traumatic Brain Injury

The cornerstone of patient care is clinical assessment by the clinician. This poses a challenge in the context of TBI, particularly when it is moderate or severe. In such a clinical context the dominant

clinical picture may well indicate cerebral dysfunction as the patient presents with an altered level of consciousness. However it may not be immediately apparent what factors are most significant in that picture – direct injury or other contributors such as reduced cerebral blood flow or tissue hypoxia. Monitoring is a critical addition to patient assessment that ideally empowers the clinician to undertake an intervention to improve the outcome for the patient.

Pulse oximetry and blood pressure measurement are the first pillars of monitoring as these are the clinical measurements most strongly associated with patient outcomes[71]. These measures are, by their nature, concerned with the global patient picture, with normalization of these parameters to a standard target associated with better outcomes. However, numerous other modalities are now being employed in hospital care of neurotrauma patients, including jugular venous bulb oximetry, direct tissue oximetry, intracranial pressure monitoring and more recently available technologies such as microdialysis and near infrared spectroscopy derived tissue oximetry.[59,84–93] To understand where near infrared spectroscopy may fit into the broader clinical picture, it is necessary to review the various monitoring options available.

Peripheral Oximetry and Blood Pressure

These two parameters have a significant amount of evidence available to underline their importance[71] Oximetry has been shown to be valuable in the management of TBI patients. Hypoxaemia has previously been shown to occur in a large number of cases, with prehospital research showing that patients with hypoxemia documented with oxygen saturations < 60% have a mortality rate of 50% compared to 14.3% with TBI but no evidence of hypoxaemia[94]. Retrospective analysis of the Traumatic Coma Data Bank has also shown that hypoxaemia occurred in 22.4% of severe TBI patients[62,63].

Prehospital and in-hospital hypotension also have a negative impact on outcomes[13]. Even a single episode of prehospital hypotension is a powerful predictor of poor outcome. As ethical considerations prohibit randomized controlled trials covering these possibilities, existing recommendations are based on large scale observational data. So while target blood pressure $\geq$ 90 mmHg is supported by at least Level II evidence[62,63], it is possible that a patient could generally have much higher blood pressures, and therefore be experiencing a degree of cerebral ischaemia at blood pressures felt to be in the acceptable range. Once in the hospital environment, patients with severe traumatic brain injury are preferentially managed with invasive arterial pressure monitoring. In addition to more responsive haemodynamic management this also facilitates derivation of further indices that may be useful in the critical care environment such as CPP, providing that ICP monitoring is also instituted.

Early research suggesting particular targets for CPP-based management emphasized the importance of maintaining CPP > 70 mmHg.[72] Therapy targeted in this manner resulted in better outcomes than an unadjusted control group in the Traumatic Coma Data Bank where ICP management was the primary therapeutic goal[95]. More recent generations of the Brain Trauma Foundation guidelines have re-evaluated this question[72].

Part of the challenge of trying to establish what should be the target ranges for CPP management is the lack of a generalizable range of normal CPP, or an agreed lower limit than can be set for all patients. Low CPP in the 50-60 mmHg range appears to be associated with worsened physiological parameters including desaturation on direct tissue oximetry and jugular venous bulb oximetry as well as cerebral microdialysis parameters associated with ischaemia. This suggests the threshold for worsened physiological parameters is in the 50-60 mmHg range.[96–98] Low CPP also correlates with worsened clinical outcome, with CPP < 60 mmHg shown to be associated with

worse outcome in a randomized controlled trial of therapeutic hypothermia in the setting of severe TBI.[99] This supported a level III recommendation that CPP < 50 mmHg should be avoided.

Although lower levels of CPP are clearly detrimental, there is not good evidence that elevating the CPP to levels of 70 mmHg and above is beneficial. Some of the earlier studies suggesting benefit from higher CPP used comparison populations without adjusting for variables in a robust fashion[95]. Some research has suggested that targeting higher CPP alone may be associated with other undesirable clinical complications, as in the study by Robertson *et al*, where the CPP therapy group with CPP maintained > 70 mmHg had no better outcome than the ICP therapy group, where CPP was maintained > 50 mmHg but ICP was specifically managed to keep it $\leq$ 20 mmHg[98] The CPP group had a risk of Acute Respiratory Distress Syndrome 5 times higher. Further studies are necessary to further define the value of targeting higher CPP along with the potential risks of that approach.

Intracranial Pressure Monitoring

Intracranial pressure monitoring provides additional information to guide patient therapy, either through medical therapy to reduce ICP or via surgical intervention. In clinical practice the two commonly used methods are insertion of an intraventricular catheter into the lateral ventricle, or an intraparenchymal or subdural microtransducer sensor[59,100]. The former is probably best considered as the “gold standard” as it measures the global ICP and offers the significant advantages of being able to re-calibrate the monitoring system and facilitate drainage of CSF for treatment of intracranial hypertension. By comparison, microtransducer monitors, while technically easy to insert, demonstrate a degree of zero drift, are more focal in their measurement of ICP and cannot be recalibrated once inserted.

From a clinical perspective, ICP monitoring offers the potential for more than display of absolute ICP alone. As discussed above, coupled with invasive arterial pressure monitoring, it facilitates targeted CPP management.[101] There is also the potential to analyse ICP waveforms themselves that may correlate with pathology and further indices may be derived such as those related to cerebrovascular reactivity[102,103].

Alternative methodologies for measuring and monitoring ICP are being actively sought. There is some preliminary work suggesting optic nerve sheath diameter assessment by ultrasound may provide an alternate means of measuring ICP. However, this methodology cannot provide information about ICP waveforms and there is mixed evidence regarding its sensitivity and specificity, with suggestions that there may be some hysteresis related to the distensibility and elasticity of the optic nerve sheath in the setting of prolonged raised ICP[104].

The Brain Trauma Foundation guidelines have included a list of indications for instigation of ICP monitoring (see *Table 1*)[105]. These represent the most widely used guidelines in clinical practice.

Level of Evidence	*Patient Findings*
II	Severe TBI∞ + Abnormal CT scan findings*
III	Severe TBI and normal CT if two or more of the following are present at admission: - Age over 40 years. - Unilateral or bilateral motor posturing. - Systolic blood pressure < 90 mmHg

∞ Severe TBI is defined as Glasgow Coma Score 3-8 after resuscitation.

* An abnormal CT is one that reveals haematomas, contusions, swelling, herniation or compressed basal cisterns.

Table 1: Indications for Intracranial Pressure Monitoring

Despite the availability of these guidelines, there remains considerable variability in actual clinical practice between institutions in terms of when ICP monitoring is employed.[106] Frequency of ICP monitoring in trauma centres appears to be associated with improved outcomes.[107,108] Introduction of protocols incorporating ICP monitoring and other advanced monitoring seems to be associated with improved outcomes compared to epochs without those protocols in place[109,110].

The Brain Trauma Foundation guidelines have reinforced the consensus that 20 mmHg represents the best point above which steps to lower ICP should be taken[111]. The actual intervention will be dependent on the individual characteristics of the patient but options include drainage of CSF, particularly in the presence of an intraventricular catheter, surgical evacuation of mass lessions or craniectomy, hyperosmotic therapy such as hypertonic saline, manipulation of CO_2 to produce cerebral vasoconstriction, or administration of anaesthetic or sedative agents to reduce $CMRO_2$.

There are no large randomized controlled trials demonstrating benefits from establishing the number 20 mmHg as a cut-off point. The largest prospective observational cohort study controlling reasonably for confounding variables analysed mean ICP in 5 mmHg increments against outcome in a logistic regression model and found 20 mmHg to have the optimal predictive value.[63] Early editions of the guidelines cite small uncontrolled series and a small randomised double-blind RCT as further support for this recommended threshold.[111]

It is, however, necessary to adjust treatment to the particular patient. Some patients may show evidence of herniation at measured ICP values less than 20 mmHg, as the location of any intracranial mass lesion will also influence the effect of the global intracranial pressure.[112,113] Likewise, some patients may tolerate higher intracranial pressures without evidence of deleterious sequelae.[114]

Cerebral Oximetry Monitoring

Oximetry monitoring aims to measure the adequacy of oxygen delivery to the brain, which can only occur in the setting of adequate cerebral perfusion. The modalities studied most extensively to date have been jugular venous bulb oximetry and direct tissue oximetry.

Jugular venous bulb oximetry requires retrograde cannulation of the internal jugular vein. This allows measurement of oxygen saturation in the blood exiting the brain[115]. Normal jugular venous oxygen saturation (SjO_2) is approximately 60%. Desaturation may be the result of systemic factors such as hypoxia, hypotension, hypocarbia or anaemia. Alternatively cerebral factors such as intracranial hypertension and cerebral vasospasm may be linked to desaturation. Elevated SjO_2

may also indicate meaningful alterations in physiology as in hyperaemia or the failure of infarcted areas to extract oxygen.

Episodes of single or multiple desaturation below 50% have been associated with higher rates of mortality compared to patients who do not have such episodes of desaturation[116]. Values higher than 75% are also associated with poorer outcomes.[117]

Jugular venous oximetry is, however, invasive by its nature. Additionally, there is debate as to whether there is an ideal side to place the monitoring or whether to sample intermittently or continuously. The right side is sampled by some on the basis that it is usually the dominant side. Some institutions test for dominancy of side, or alternatively measure the side that is most injured. Monitoring of both sides can be associated with variability, raising the question of whether values can be assumed to be indicative of the whole brain perfusion-metabolism balance. [86]

Direct tissue oximetry is another invasive option for deriving information relating to brain tissue. Available devices require insertion of an intraparenchymal probe of 0.5-0.8 mm thickness.[86] Complication rates are comparable to those for intraparenchymal ICP monitors. Once the probe is inserted, an initial sampling period of 1-2 hours should be disregarded before applying the derived information to clinical monitoring to provide some confidence that data produced thereafter are accurate.

Case series involving relatively small numbers of subjects have demonstrated that low levels of brain tissue oximetry ($P_{bt}O_2$) are associated with higher mortality. In a series involving 34 patients, increasing time spent below a threshold of 15 mmHg was associated with increased mortality[118]. A separate series with 35 patients, all with severe TBI, showed that those with

$P_{bt}O_2$ < 10 mmHg for more than 30 mins had inferior rates of good outcome as defined by Glasgow Outcome Score 4-5 (22% vs 73%) as well as far higher mortality rates (56% vs 9%).[119] Similar findings were reported by van den Brink *et al*. in a prospectively collected samples of 101 patients.[120] This study also found that $P_{bt}O_2$ < 15 mmHg for 4 or more hours was associated with a 50% risk of death.

Monitoring values within the initial 72 hours appear to correlate with outcomes. Eriksson *et al* have clearly demonstrated that survivors have consistently higher $P_{bt}O_2$ measurements over the first 72 hours of admission when compared to those who do not survive their injuries.[121] This was apparent despite the fact that neither ICP and CPP were significantly different over the period of the trial. In this research, regression tree analysis was used to identify 29 mmHg as a more appropriate target for neurotrauma management.

Further research is required to establish whether therapy targeting increased $PbtO_2$ results in better outcomes. The main study suggesting improved mortality included historical controls with substantially worse outcomes than is expected in modern hospital care.[122]

Cerebral Microdialysis

This methodology may be used to monitor brain tissue biochemistry in the neurointensive care setting[88]. The thin microdialysis catheter (diameter 0.6 mm) may be inserted as a stand alone monitor, or introduced as part of a triple lumen device incorporating ICP monitoring and tissue oxygen sensors. The catheter consists of a probe with two lumens with the tip containing a semi-permeable dialysis membrane placed in the tissue of interest. A microdialysis pump delivers artificial CSF through the interior of the catheter. This equilibrates with the interstitial tissue

around the catheter. At standardised flow rates the concentration of glucose, lactate, pyruvate and glutamate in the dialysate becomes approximately 70% of the concentration in the interstitial fluid (ISF). Samples are continuously collected into microvials that are analysed at the bedside. Results are displayed as trend curves.

The utility of cerebral microdialysis is to detect early changes in chemical markers of ischaemia. The hope is that this will then allow early initiation of targeted therapy to reduce secondary damage to vulnerable cerebral tissue. The key change in TBI is an elevated lactate/pyruvate ratio which can be detected at the bedside before evidence of increased ICP if the catheter is placed in an area near injury.[123] Other changes that may be seen are a fall in measured glucose and an increase in glutamate and glycerol concentrations.

As a measurement methodology, monitoring local tissue biochemistry offers pros and cons. In areas of cerebral tissue at risk, such as in the penumbra around an area of bleeding, microdialysis catheters may offer an early warning of impending ischaemia. However if the catheter is placed in an area of normal tissue changes may only be detected late and normal biochemical results may produce false reassurance.

Consensus guidelines therefore suggest that in the setting of diffuse injury a catheter may be placed in the non-dominant frontal region.[88] Where there is a focal mass lesion one catheter should be placed in pericontusional tissue and a second may be placed in normal tissue.

Understanding Near-Infrared Spectroscopy Tissue Oximetry Monitoring

Near-Infrared Spectroscopy Tissue Oximetry Monitoring as a Potential Ideal Monitor

The hypothetical ideal monitor of oxygenation or perfusion has been described with the following characteristics[124]:

1. Non-invasive.
2. Harmless.
3. Continuous, with high temporal resolution.
4. Robust and artefact free.
5. Absolute calibration to known reference points.
6. Reproducible.

Present monitors seeking to add to the understanding of oxygenation and perfusion of cerebral tissue do not meet this ideal. SjO_2 and $P_{bt}O_2$ are both invasive and potentially associated with harm. MAP and peripheral oxygen saturation provide information about global conditions but do not directly address the tissue of interest. Additional monitors required to calculate CPP by providing a measure of ICP are invasive and in the case of intraparenchymal monitors cannot be recalibrated.

Near-infrared spectroscopy (NIRS) tissue oximetry can be instituted with non-invasive sensors or optodes applied at the skin surface over a tissue of interest. Evaluating the potential to meet the other ideal criteria requires some understanding of the underlying technology.

The Behaviour of Near-Infrared Light in Tissues

Near Infrared Spectroscopy (NIRS) relies on the application of the behaviour of light in a medium. The particulars of the way this behaviour is exploited are dictated by the wavelengths of light employed and the characteristics of the medium – human tissues.

Near Infrared Spectroscopy (NIRS) was initially described as a technique with potential for assessing enzyme redox state in 1977 by Franz Jöbsis[125]. While the principles of utilising the detection of light after shining it into a tissue have been utilised in other modalities such as pulse oximetry, there are some specific characteristics to light in the near infrared spectrum and its interaction with tissues that are relevant to its use in clinical settings. Recent generations of device have improved the accuracy of detection and the time frame to obtain readings.

Understanding the derivation of NIRS technology requires consideration first of behaviour of light in simple media. Bouguer first described the behaviour of light incident upon layers of homogenous material of equal thickness in 1729, noting that as each layer of an equal thickness was placed between the emitter and the detector, the amount of light detected decreased by a predictable proportion, allowing calculation of an absorption coefficient.
Later work by Beer described the relationship between the absorber coefficient and the absorber concentration where the absorber is dissolved in a solution that does not absorb any of the incident light. The light attenuation seen in this situation is directly proportional to the concentration of the absorber in the solution.

The result is a modification of the original Lambert-Bouguer law, expressed as:

$$I = I_0 e^{-\mu a.d}$$

where I = the transmitted intensity of light of initial density I_0 after it has passed through a homogenous absorber with an absorption coefficient μa over distance d.

Given that the absorption coefficient μa is understood using the Beer modification to constitute the product of α, the specific absorption coefficient of the absorber and c the concentration of the solute, the Beer-Lambert law is described as:

$$I = I_0 e^{-\alpha cd}$$

The behaviour of light in tissues is still more complex than this description. The Beer-Lambert law assumes that all incident light is either absorbed or transmitted. This is not the case in complex media. In addition to transmission and absorption, some light will be reflected back to the emitter and some will be deflected away from the initial path. This phenomenon is created by the reality that any photon passing through the tissue will confront multiple boundaries between different media. At each boundary any degree of mismatch between the refractive indices of the two media will result in some combination of transmission, absorption and scattering.

The end result is that the amount of light arriving at a detector at a point distant to the emitter will be determined by a number of interactions along the way:

1. Absorption by substances in keeping with their absorption coefficient.
2. Reflection at optical boundaries between media with different refractive indices.
3. Scattering of light.

Scattering is the predominant mechanism by which attenuation occurs in tissues, accounting for around 80% of the observed difference. Absorption accounts for the majority of the remaining 20%.[126]

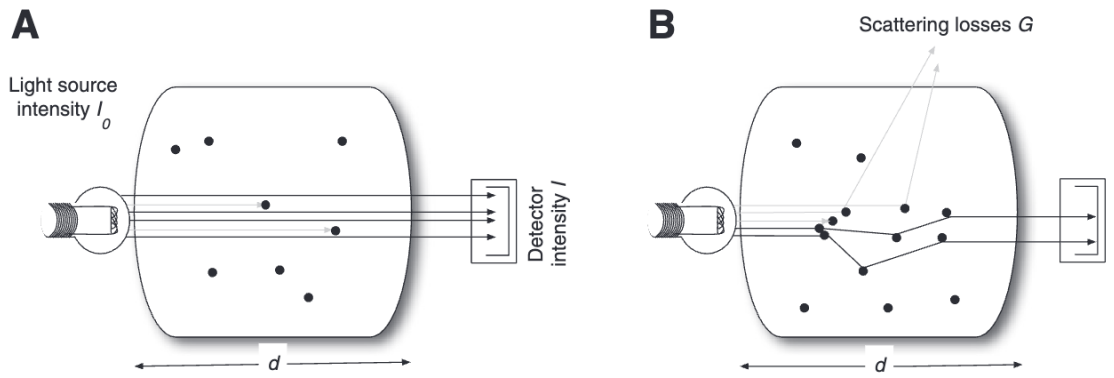

Figure 6: Diagrammatic representation of the effects of light scattering in biological tissue. A represents the idealised situation where light attenuation between a source and detector is dependent only on its absorption by chromophores. B depicts a situation more representative of behaviour in biological tissues with scattering increasing the path length of emitted photons. [Reproduced from Ghosh et al. with permission.][91]

A further factor not dealt with in the Beer-Lambert law is the increase in distance travelled by any photon to reach a detector after it progresses through a series of interactions along its journey. Instead of a single distance, *d*, defining the travelled distance, it is necessary to consider the *Differential Path Length* (DP) of a photon as it travels from emitter to detector. The scaling factor between DP and *d* is known as the Differential Pathlength Factor (DPF).

The modified Beer-Lambert law is therefore expressed (in log base 10 form) as:

$$A = \log_{10}(I_0/I) = \varepsilon.c.d.DPF + G$$

where A = attenuation (known as optical density in log base 10), ε is the specific extinction coefficient, c represents solute concentration, d equals thickness of the media, G is light attenuation due to scattering and background absorption.

The NIR spectrum is described as lying between 650-950 nm. Most tissues are effectively transparent to wavelengths of light in this part of the spectrum. This allows photons to pass through with minimal interaction with local tissues. Critically there are specific chromophores that do significantly interact with near-infrared spectrum light and it is the interaction between near-infrared light and these chromophores that underpin the utility of NIRS in clinical monitoring.

Specific molecules interact very differently with light at different wavelengths. NIRS systems therefore utilise different wavelengths to minimise the impact of non-relevant chromophores. Additionally, over the time frames involved in monitoring of biological signals, some of these chromophores can be considered to be present in fixed concentrations.

Chromophores that can be considered to be present in fixed concentrations include water, lipids and melanin. While water is present in high concentrations in tissues, it remains relatively transparent in the near-infrared range. The degree of absorption would increase substantially at 1700 nm for water.

Lipids absorb near-infrared light at relatively low levels but are potentially relevant in subcutaneous tissues and in myelin encasing nerves. Given the low amount of subcutaneous lipids in monitoring locations relevant to cerebral tissue interrogation they are less of an issue for cerebral oximetry monitoring compared to some other areas. Some muscle beds may have significant overlying subcutaneous lipid deposits and therefore present a different challenge.

Melanin is present throughout the epidermis and its structure can produce scattering. While its tendency to produce attenuation is most marked in the 200-400 nm range, part of the ultraviolet region, hair or significant amounts of melanin can produce substantial attenuation.

Unlike these absorbers that are present in consistent concentrations and interact with incident near-infrared light in a consistent fashion, there are chromophores with clinical utility because their absorption behaviour alters depending on their redox state.

The first of these is haemoglobin (Hb). Binding of oxygen to Hb induces a distinct change in the shape of the molecule. These two forms of the molecule, oxy- and deoxyhaemoglobin, display different absorption characteristics with near-infrared light. This creates the capacity to differentiate between the amounts of each molecule within a sampled area of tissue. Wavelengths between 700 -850 nm are most frequently utilised as it is in this range that the absorption spectra of oxy- and deoxyhaemoglobin are most distinctly different.

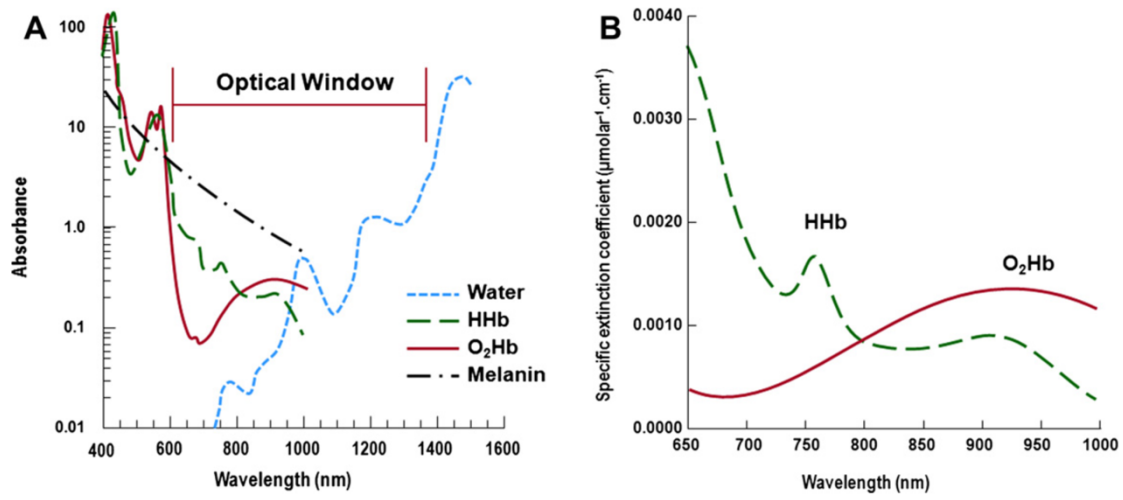

Figure 7:Light absorption spectra of different absorbers in tissue. (A) shows the optical window, the range over which wavelengths of light interact with chromophores. (B) highlights the differing extinction coefficients of oxy- and deoxyhaemoglobin at specific wavelengths in the near-infrared spectrum. [Reproduced from Pellicer et al. with permission.][126]

Cytochrome C oxidase, a critical enzyme in the electron transport chain within mitochondria, is another molecule displaying different absorption spectra in the near-infrared spectrum for the oxidised and reduced molecules. The total concentration of cytochrome c oxidase may be assumed to be constant over the time period involved in clinical NIRS monitoring. This means that changes evident at the detector can be taken as reflective of a change in the redox state of cytochrome c oxidase. The challenge in utilising this observed behaviour clinically when it comes to cytochromes is that the relative concentrations of these molecules are low in sampled tissues.

Turning Principles into Monitoring

The original work by Jöbsis published in 1977 utilising wavelengths of 760 nm and 815 nm in cat heads, dog heart and human head models.[125] In this work Jöbsis established the concept of a "near infrared optical window" into tissue with the capacity to interrogate oxygenation states in organ and tissue 1-3 cm below the skin surface.

However Jöbsis utilised a transillumination technique which cannot be applied to the brain or other clinically relevant measurements in humans. For human clinical use it is necessary to utilise a reflectance spectroscopy approach where the emitter and detector are 1cm to 4 cm apart within a single sensor. Some photons emitted into the tissues will be reflected back to the detector. It is these reflected photons that are then utilised to determine measurements of chromophores such as oxy- and deoxyhaemoglobin.

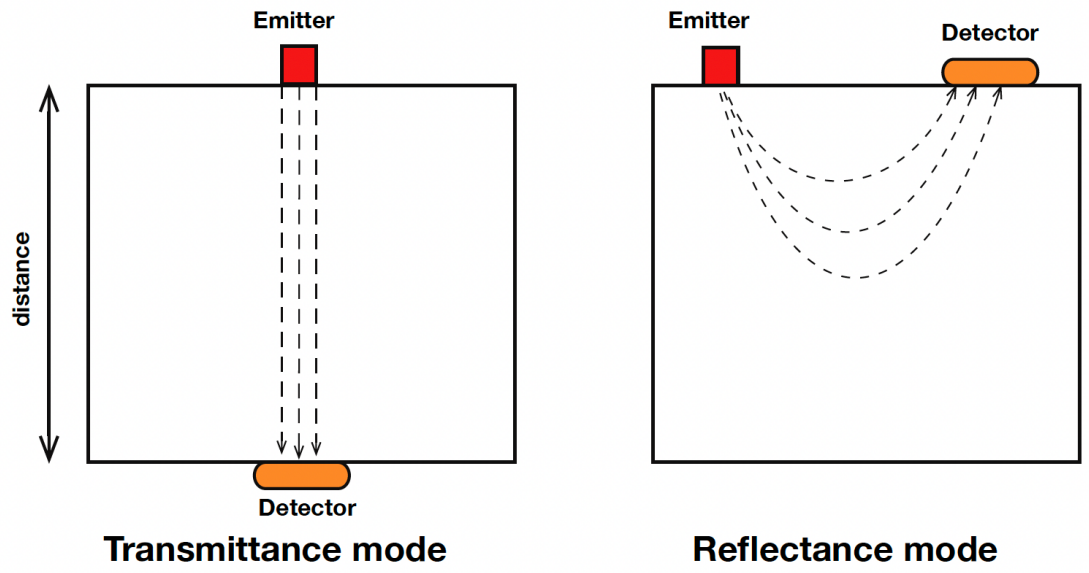

Figure 8: Representation of transmittance vs reflectance utilisation of spectroscopy.

To utilise the underlying principles of NIRS in a commercial monitor, manufacturers deploy variants of a technique called continuous wave (CW) spectroscopy. The devices continuously shine a beam of near-infrared light into the tissue of interest from an emitter. Reflected light must then be picked up by a detector so that can signals can be processed to generate oxygenation metrics.

This implementation alone cannot provide absolute Hb concentrations in tissue and oxygenation measurements would rely on assumptions regarding DPF, absorption or scattering coefficients. Two similar CW approaches are used to enhance the ability to discern clinically useful measures of oxygenation. These approaches are the multi-distance approach and spatially resolved spectroscopy (SRS) and both may be combined within one monitoring system.

In the multi-distance approach, a single light source is positioned 1-3 cm away from a series of detectors arranged in increasing distance from the emitter. As each detector has a different source-

detector separation there is the ability to allow wavelength-specific measurement of light attenuation as a function of that separation.

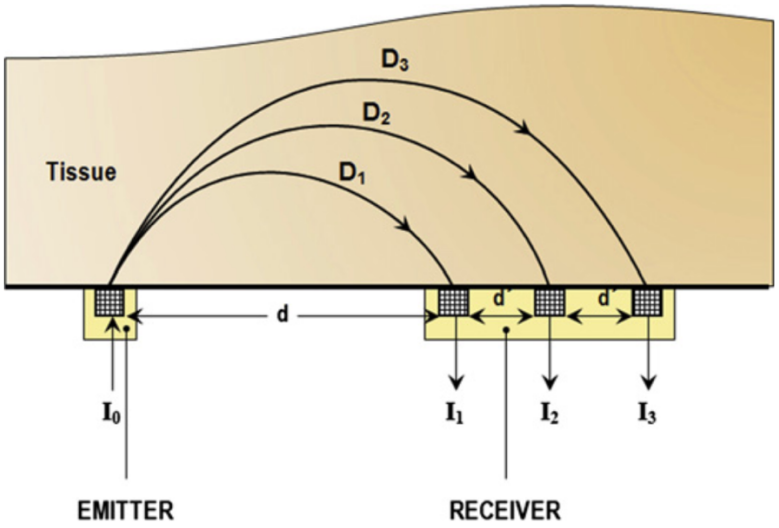

Figure 9: Spatially resolved spectroscopy with multiple detectors displaced from the emitter. [Reproduced from Pellicer et al. with permission.][126]

SRS describes an approach that seeks to provide different depths of interrogation. This is designed to minimise the issue of contamination of measurements by signals returning from superficial tissues. Increasing the distance between the emitter and detector is also part of improving this situation though there is still evidence that signal contamination by superficial tissues may be an issue.[127] SRS incorporates two or more detectors in the same sensor creating a situation where there is more than one emitter-detector distance. In effect the closer detector provides information from a superficial pathway between emitter and detector which can then be considered as representative of the superficial tissue. This information can then be effectively removed in processing from the "deeper" pathway to ensure that this measurement, which should reflect the tissue of interest, has had the contribution of superficial contamination removed.

There are additional techniques that are approaching clinical utility where they were once confined to research settings. Frequency-resolved spectroscopy (FRS) modulates the intensity of light emitted at a known frequency with both the phase shift and degree of light attenuation measured to determine information regarding the time of flight of photons through the sampled tissue. This is then used to calculate absolute values of absorption and scattering coefficients which can then be used to derive absolute concentrations of key chromophores including oxy- and deoxy-haemoglobin along with haemoglobin oxygen saturation.

Time-Resolved Spectroscopy (TRS) involves generation of brief pulses of laser of around a picosecond duration to directly measure the transit time of photons through tissue. This allows calculation of an accurate measure of the DPF and therefore permits calculation of absolute Hb levels and Hb oxygen saturation levels.

A key issue with the range of options available is that companies producing commercial monitors employ these techniques as part of bespoke solutions, rather than an agreed standard. With multiple companies providing their own machine for the clinician to consider (CASMED marketing the Fore-Sight™ system, Nonin producing the Equanox™ device, Covidien offering the INVOS™ system and Hamamatsu delivering the NIRO™ series) there is significant variety in approaches employed in the absence of a gold standard. Even within a particular company's approach, different sensor sizes are part of the approach to deal with infants, paediatric patients and adults as well as differences in the processing of the raw signal. Comparison between devices is difficult enough, but even within a single commercial offering it has been demonstrated that adult vs paediatric sensors may produce a difference in displayed tissue oximetry value of up to 15%.[128]

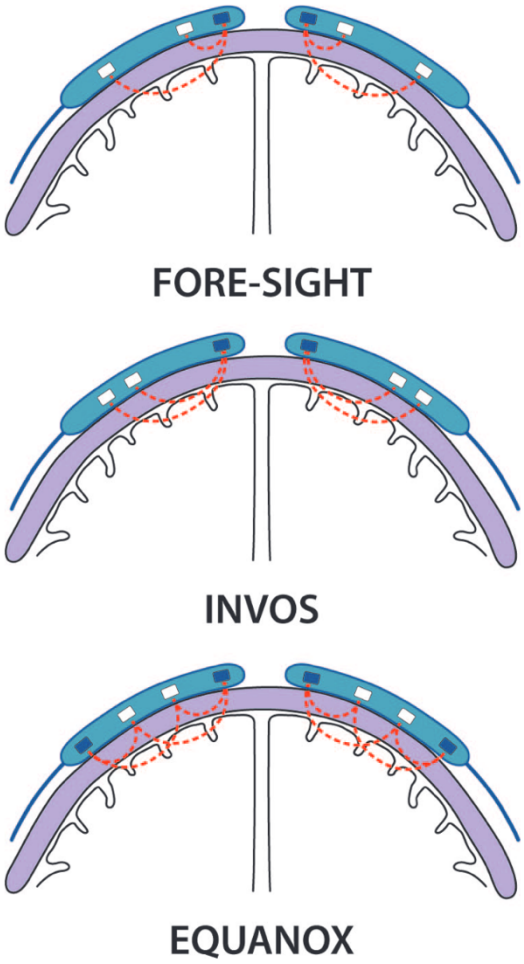

Figure 10:Examples of different optode designs from commercial manufacturers to produce spatially resolved spectroscopy. [Reproduced from Davie et al. with permission.][129]

The varying approaches amongst manufacturers introduce an additional pragmatic issue. Manufacturers allocate different labels to measurements essentially presented as providing the same information. Thus the measure of tissue oxygenation may be presented as rSO_2, StO_2, $S_{ct}O_2$ and TOI. The measure correlating with total haemoglobin in the sampled area of tissue may be reported as either HbT or HbI and deoxyhaemoglobin is sometimes described as HHb or HbD.

For simplicity in this thesis, the measure of tissue oxygenation is presented as rSO_2 and the measure of total haemoglobin in a tissue is presented as HbI.

Challenges Applying Near-Infrared Spectroscopy in the Clinical Environment

The physics underpinning the behaviour of near-infrared light in tissues is well understood but the steps then required to bring that understanding to the bedside are accompanied by a range of limitations. These need to be understood by the clinician and that may still create troubling confounders. The variability when comparing different machines has been previously demonstrated, as in the study by Bickler *et al* where 5 different systems were applied to adult volunteers where hypoxic challenges were monitored through NIRS oximetry along with invasive measures of arterial oxygen saturation and SjO_2. While all oximeters picked up desaturation there was significant variability in the measurements displayed. [130]

Multiple elements can contribute to the variability seen in the clinical setting. The key issues are:

1. Absence of a reference standard and robust calibration
2. Algorithm variance.
3. Real world confounders such as ambient light and pigments that may act as chromophores in skin.
4. Managing superficial signals.

There is no specific gold standard against which NIRS tissue oximetry can be validated. The ideal approach would be to evaluate the performance of NIRS oximetry against a simultaneous direct measurement correlating to the same target area of monitoring. This is not possible given that NIRS is effectively interrogating tissue remotely in an area where direct measurement cannot be feasibly applied to act as the benchmark.

The lack of a gold standard leads to the use of surrogates for calibration. Most commonly this can be described as:

$$rSO_2 = (0.25) \times SaO_2 + (0.75) \times SjO_2$$

where rSO_2 = tissue Hb saturation, SaO_2 = arterial oxygen saturation and SjO_2 = jugular venous oxygen saturation.

The constants applied here, 0.25 and 0.75, are derived from the assumed relative contributions of arterial and venous blood to the total blood volume in the brain. While there has been work testing this correlation of this assumption with the true picture and with SjO_2 and central venous oxygen saturation, there is still significant variability.[131–134] Assuming a constant ratio between arterial and venous blood does not reflect true physiology as this relationship is constantly shifting and is not regarded as a good method for validation.[135] The study by Bickler *et al* highlighting variability in the response to hypoxia notes that this assumption does not reflect the dynamism of the patient state and represents one possible explanation for the variance observed.

Algorithm variance is a significant issue not just because it is the result of inevitable different approaches between manufacturers but also because the different choices made are essentially hidden from clinicians and researchers. There is a critical step between measurement of light attenuation and display of derived values that is dependent on the approach to the algorithm employed within the machine. Examples of nonproprietary algorithms have been extensively described previously.[136] Such an analysis is not feasible when it comes to commercial monitors as manufacturers do not provide open access to their particular algorithms. Algorithmic choices can have significant implications with Metz *et al* demonstrating that making slightly different

assumptions regarding absorption and scattering coefficients can have a measurable impact on calculated rSO_2 values. The degree of variation also differed according to whether the patient was an adult or neonate and with interrogation of cerebral or muscle tissue beds.[137]

Real world confounders are also relevant to the clinician, particularly in the prehospital environment. Hair is of specific significance as a confounder in cerebral oximetry and manufacturers suggest limitation to the forehead as a result.[138] The implication is that areas of the cerebrum remote to the frontally-placed sensors cannot be directly interrogated and only the influence on those areas of global changes in cerebral oximetry can be inferred.[139] Challenges as diverse as skin colour, sensor adhesion and presence of other potential chromophores such as bilirubin can all significantly influence displayed measurements.[126,140,141]

A particular real-world confounder that is a substantial concern in exploring prehospital use is ambient light. There is evidence that different machines available on the market respond differently to the challenge of exposure to ambient light which may influence displayed values or result in an inability to provide measurements. This has been suggested both in exposure to natural light while in an operating room and in our own early evaluation of performance of the Foresight™ in ambulance and helicopter settings.[3,142] In the benchtop study by Zaouter *et al* there was at least a suggestion that the Foresight™ device, which utilises more wavelengths than the INVOS™ or Nonin systems also tested, may be less influenced by ambient light.

Finally, as noted above, dealing with the challenge of confounding superficial signals has been the focus of extensive effort by manufacturers. There is clear evidence that this has not entirely removed the problem as shown by altered oximetry readings in the context of occluding superficial scalp flow or producing a reduction in scalp blood flow with vasoconstricting agents.[127,143,144]

Summary of Near-Infrared Spectroscopy Tissue Oximetry Monitoring

Near-infrared spectroscopy tissue oximetry monitoring is a potentially useful application of physics that is well understood. With each generation of machine, substantial efforts have been made to address potential confounders such as superficial contamination and precision of oximetry measurements as more wavelengths are utilised and sensor design improves, though some of the sources of improvement are hidden from clinicians by closed systems.

These enhancements are welcome though the ongoing issues of potential confounders cannot be forgotten by the clinician. Although manufacturers have taken to describing modern NIRS oximetry devices as providing "absolute oximetry" there is substantial intra- and interindividual baseline variability with the normal displayed range of rSO_2 falling somewhere between 60-75% with the coefficient of variation for absolute baseline values being around 10%.[145]

This is not to suggest that all this effort to solve the challenges posed by a promising technology first described in 1977 has produced nothing. When evaluated against the characteristics of the ideal monitor to measure oxygenation and perfusion NIRS tissue oximetry satisfies 3 core criteria – being noninvasive, harmless and continuous with high temporal resolution – immediately. The inability to provide absolute calibration will remain an issue that requires both understanding and consideration from the clinician and argues for the use of NIRS tissue oximetry as a trend monitor providing useful insights with high temporal resolution.[91] The case is then clear that there is a need to evaluate whether this technology can provide robust and artefact free monitoring data in a reproducible fashion.

The work of this thesis commences at a point where some evidence is available across a range of clinical settings but there is a clear need for further exploration.

Near-Infrared Spectroscopy Across Clinical Settings

The display of rSO_2 offers a single number, oxygen saturation in the tissue, to simplify the contribution of multiple physiological variables. This parameter could be simply described as a percentage measure of the proportion of Hb within a volume of sampled tissue which is oxygenated:

$$rSO_2 = \frac{HbO_2}{HbO_2 + HbD}\ x\ 100$$

where HbO_2 is oxyhaemoglobin and HbD is deoxyhaemoglobin.[138]

A more comprehensive representation which makes it easier to appreciate the number of contributors to rSO_2 which is ultimately a reflection of the balance between delivery and consumption provides clarity as to the range of factors underlying the final displayed value and the multitude of parameters that could therefore be manipulated to influence that number:

$$StO_2 = (art\% \cdot SaO_2) + \left(vein\% \cdot \frac{\left(\frac{SaO_2}{100} \cdot Hb \cdot 1.34\right) - \left(\frac{CMRO_2 \cdot 100}{\frac{(MAP\text{-}CVP)}{SVR}}\right) \cdot 100}{Hb \cdot 1.34} \right)$$

art% here represents the percent contribution of the arterial component while *vein%* represents the equivalent for the venous component.

Arterial oxygen saturation (SaO_2) will be influenced by respiratory parameters including gas exchange in the human. The level of Hb will clearly be contingent on the patient's baseline but in the clinical setting may also be significantly altered in situations of blood loss or when transfusions are being administered. $CMRO_2$ will clearly be influenced by the activity in the cells and this parameter will change if those cells are not metabolically active in the context of hypothermia, injury or anaesthesia. CBF is a function of MAP, CVP and SVR at a systemic level but as described earlier will be significantly influenced by autoregulation (or the loss of autoregulation) and arterial CO_2.

All of these parameters are routinely altered in a variety of clinical situations across surgery, acute illness and trauma and entirely amenable to therapeutic intervention. This has led to research in all of these fields in an attempt to establish meaningful threshold values of rSO_2 and to start

developing approaches to respond to values felt to be abnormal with the goal of improving patient condition and ultimately patient outcomes.

Cardiac Surgery

Cardiac surgery is classified as high-risk surgery. One of the reasons for this is the high rate of neurological complications. In adult patients there is a 1-3% rate of stroke and more than 50% of patients suffer long-standing postoperative cognitive dysfunction.[146] Initial retrospective studies to examine the role of NIRS oximetry in cardiac surgery suggested there was reason to be optimistic that inclusion of cerebral oximetry might allow detection of clinically meaningful cerebral desaturation and reduce the incidence of permanent stroke.[147,148]

Given that multiple of the elements contributing to low rSO_2 can be addressed during cardiac surgery, algorithms to guide a response to desaturation can be defined.[149] However prospective studies exploring whether instituting therapy to reverse cerebral desaturation results in better patient outcomes have not shown clear benefits.

Slater *et al* undertook a prospective study with a defined approach to maintain rSO_2 in 265 patients having coronary artery bypass grafting.[150] Ultimately the study confirmed that a significant period of cerebral desaturation was associated with postoperative cognitive decline and increased hospital length of stay, but no improvement in outcome was seen when steps were taken to address cerebral desaturation. The association of cerebral desaturation with postoperative cognitive decline was established by evaluating the “desaturation dose” (calculated as the product of length of time and depth of $rsO_2 < 50\%$) that operated as an independent predictor of postoperative cognitive decline. A desaturation dose of 3000 second.% had an odds

ratio of 2.22 (P = 0.048) for postoperative cognitive decline and it is notable that there was no evidence of significant postoperative cognitive decline in patients who did not reach the 50% rSO_2 threshold.

It is important to note that the intervention was not successful in restoring rSO_2 in all patients in the intervention group. This work implies that there is a critical point at which the product of degree of desaturation and the duration of cerebral desaturation lead to damage that results in functional impairment. This is coherent with the observations in animal research published around the same time.[151] The area that requires more work is defining how to most effectively restore cerebral desaturation once the deviation is observed.

A strategy explored by Murkin *et al* to maintain rSO_2 at 75% of preoperative values showed no reduction in stroke incidence or mortality after cardiac surgery[152]. This study involved a control group where NIRS oximetry values were obscured from the treating team and an intervention group where values were displayed and intervention to maintain or restore rSO_2 was allowed. In the control group it was the case that significantly more patients died or developed major other organ morbidity. This was also associated with a lower baseline and mean rSO_2, as well as more episodes of intraoperative cerebral desaturation, and both longer intensive care unit and hospital length of stay. These studies may have been underpowered to show significant differences in neurological outcome.

Interestingly, preoperative assessment may be aided by cerebral oximetry prior to cardiac surgery. A prospective observational study of 1178 patients undergoing cardiac surgery involving cardiopulmonary bypass intraoperatively showed that low preoperative cerebral rSO_2 was associated with higher postoperative biomarkers of cardiac and renal injury along with worse

cardiac dysfunction.[153] Preoperative values were also lower in those who had died in 30 days, and values < 50% were an independent risk factor for both 30-day and 1-year mortality. The suggestion is that low preoperative rSO_2 provides a surrogate measure of other organ perfusion that can be associated with subsequent outcome. The authors suggested that preoperative rSO_2 was a useful risk stratification tool prior to cardiopulmonary bypass, operating as an indirect way of assessing other organ perfusion.

Carotid Endarterectomy

Carotid endarterectomy involves a period of occlusion of the internal carotid artery. This creates a period of high risk of cerebral ischaemia particularly if there is any limitation to collateral circulation via the Circle of Willis. This risk has previously been managed by placement of a shunt to maintain flow, although this produces its own risk of stroke related to clamping and shunt placement.

To minimise the risk of shunt-related stroke monitoring of adequacy of blood flow has been included in carotid surgery, allowing placement of a shunt only where there is evidence of compromised cerebral perfusion. Monitoring techniques utilised include transcranial Doppler ultrasonography, electroencephalography, carotid stump pressure monitoring or surgery under local anaesthesia to permit continuous neurological assessment. The last of these is considered to be the gold standard for monitoring although none of the described options entirely remove the risk of stroke.

NIRS oximetry was tested against clinical neurologic examination by Samra *et al* by retrospectively analysing 94 cases of carotid endarterectomy performed under regional anaesthesia and

comparing patients who developed symptoms of cerebral ischaemia with application of carotid cross-clamp to those who did not develop neurological symptoms.[154] The 10 patients who developed symptoms of cerebral ischaemia had a significantly greater reduction in rSO_2 from baseline compared to those with no such symptoms. The authors undertook logistic probability analysis and suggested that reduction in rSO_2 of 20% from baseline provided an optimal sensitivity-specificity balance.

Subsequent research in 594 patients under general anaesthesia having carotid endarterectomy utilised receiver operating characteristic analysis to define an 11.7% reduction from baseline as the optimal predictor of neurological dysfunction.[155] A further study conducted under general anaesthesia compared StO_2 monitoring values generated by a NIRO-300^{TM} device to EEG evidence of ischaemia.[156] There was no patient with a reduction in tissue oxygenation index < 13% that demonstrated EEG changes consistent with ischaemia. Specificity was 93%.

NIRS appears to offer equivalence to other monitoring modalities in this clinical context though it has not been established as superior. There appear to be practical advantages in ease of use, operator independence and temporal resolution when compared to other options such as transcranial Doppler ultrasound or sensory evoked potentials.

NIRS and Head Injury

Initial research utilising NIRS in TBI was just as interested in providing a rapid screening assessment of potential haematoma as in defining more subtle changes in tissue oxygenation. The presence of changes such as haematoma or intracranial blood, subarachnoid blood or cerebral oedema will fundamentally change the absorption characteristics of the tissues through which photons are

passing. This variation has been exploited to assist with the detection of intracranial haematoma and cerebral oedema.

The accuracy of NIRS oximetry techniques in detecting haematomas has been explored in small prospective studies. A device utilising NIRS oximetry technology displayed a sensitivity of 87% for detecting intracranial haematomas when compared to subsequent cerebral imaging with CT or MRI.[157] Although 4 of the 30 cases did not display a difference in monitoring values, all of those patients had chronic subdural haematoma. In this study, the NIRS device utilised was a prototype handheld device capable of displaying a difference in absorption characteristics between the two hemispheres when placed to derive readings from the right, then the left side of the head. NIRS-derived tissue oximetry of this nature has also been shown to detect delayed development of haematoma in the hospital setting.[158]

Early observational studies relating to ischaemic thresholds yielded inconsistent results. An observational study in 18 patients utilising an INVOS oximeter demonstrated an association between increasing time spent with rSO_2 values below 60% and compromised cerebral perfusion pressure, raised intracranial pressure and mortality.[159] A more recent study compared direct tissue oximetry ($P_{bt}O_2$) with non-invasive NIRS oximetry in the 16 hours after severe TBI. rSO_2 < 60% was moderately accurate for predicting severe brain hypoxia (defined as $PbtO_2$ < 12 mmHg) with a sensitivity of 73% and specificity of 86%.[92] Sensitivity and specificity for detecting moderate brain hypoxia (as defined by PbtO2 of 12-15 mmHg) was much poorer at 62% and 49% respectively. The authors conclude that NIRS oximetry does not substitute for direct brain tissue oximetry. This is reasonable, although given the sampling sites are different and the operating physiological variables are not the same, it is not unexpected.

The utility of NIRS techniques in the setting of TBI may benefit from the addition of parameters beyond rSO_2, and HbT. Including measures of metabolic failure by monitoring cyctochrome oxidase levels may lead to the ability to determine the ischaemic threshold after brain injury. Early exploration of the potential to incorporate monitoring of cytochrome oxidase levels into assessment of patients with TBI or establishment of threshold values that correlate with ischaemia have occurred at a small scale but are not a feature of clinical practice at commencement of these projects.[160,161]

NIRS and Evaluation of Cerebral Autoregulation

An additional area of exploration has been in assessment of cerebrovascular autoregulatory status in a variety of clinical settings or pathophysiological states. Some of the earliest examples of such exploration include after subarachnoid haemorrhage, TBI, and cardiac surgery. [103,162–165] The hope is that continuous monitoring of cerebral autoregulation might help both with prognostication and guide targeted adjustments of MAP and CPP to levels optimal for the individual patient and thereby minimise secondary injury.

The initial steps have been to derive measures of cerebrovascular reactivity as a surrogate for cerebrovascular autoregulation. This relies on analysis of the slow waves (in the 0.05-0.003 Hz range) that can be seen in CBF, cerebral blood volume (CBV) and oxygenation. These slow waves arise because the myogenic, metabolic, and neuronal mechanism that exert an influence on the tone of cerebral vessels all operate on different time scales. Indices designed to reflect cerebrovascular reactivity have been derived not just from analysis of NIRS variables but also from work with ICP, transcranial Doppler flow velocity in the middle cerebral artery and $P_{bt}O_2$.[162,166–172] The focus on evaluation of a surrogate measure, cerebrovascular pressure reactivity, rather

than direct assessment of cerebral autoregulation is pragmatic. Direct assessment would require approaches such as as Positron Emission Tomography (PET) which by its nature is not practical for patient monitoring and cannot provide continuous information.

When analysis is undertaken to correlate the slow waves in ICP and arterial blood pressure, the derived index is the Pressure Reactivity Index (PRx). At a theoretical level, if cerebral autoregulation is intact then when arterial blood pressure rises, cerebral vasoconstriction should occur which therefore maintains a constant CBV and no change in ICP would be expected. If cerebral autoregulation is absent, the rise in arterial blood pressure will elicit no cerebrovascular response and there will be a resultant increase in CBV and ICP. For PRx, a positive value indicates the cerebral vessels are passive and non-reactive whereas a negative value of PRx suggests the vascular bed with slow waves in arterial blood pressure provoking inversely correlated slow waves in ICP.[169]Not only has PRx been demonstrated to reflect global cerebrovascular reactivity, disturbed reactivity as indicated by a positive value for PRx has been shown to be associated with lower GCS at admission, poorer functional outcome and higher ICP.[169]

Earlier published work by Czosnyka *et al* utilised transcranial Doppler ultrasound to establish indices relating to middle cerebral artery (MCA) blood flow.[171] In this case while ICP was monitored continuously with an intraparenchymal monitor and arterial pressure was measured invasively, MCA insonation was undertaken on a daily basis for 20 minutes to 2 hours. The key variables utilised for correlation were the transcranial Doppler flow velocity (FV) during cardiac systole (FVs) and as a time-averaged mean (FVm). From this the correlation coefficient index between FVm and CPP was derived (Mx) along with the equivalent for FVs (designated as Sx). Both Mx and Sx were significantly correlated with patient outcome and GCS score on admission.

This study also found that patients with poor outcome had a positive Mx over the first 2 days after injury, indicating poor autoregulation. They then had a significant loss of autoregulation during days 6 to 8 after a period of intact autoregulation during days 3 to 5. Another interesting finding was that in 6 of the 82 patients included in the study there was evidence that autoregulation was disturbed even when CPP was > 70 mmHg. Outcome was unfavourable in these patients. A finding that cerebral autoregulation can be disturbed despite CPP being in the range considered "optimal" is significant for clinicians.[72] Management guidelines suggest that targeting of CPP in an optimal range is the most that can be practically done to limit secondary injury. Being able to define groups where 'optimal CPP' appears to be inadequate would help define a group where targeting autoregulation itself by some means could make the difference between a poor outcome and the best possible return of function.

The potential to use $P_{bt}O_2$ to derive indices of autoregulation has also been explored.[172] Jaeger *et al* defined the index ORx by calculating the moving linear Pearson's correlation coefficient between values of CPP and $P_{bt}O_2$ obtained every 30 seconds. ORx at 1 showed the best correlation with patient outcome and also with PRx, which was calculated as described above.

NIRS tissue oximetry offers a different option to consider indices of cerebral blood volume. NIRS provides a measure of total Hb, HbT which is the sum of oxyhaemoglobin and deoxyhaemoglobin concentrations. It also provides regional cerebral tissue haemoglobin oxygen saturation (rSO_2). NIRS slow wave activity can be seen in both HbT and rSO_2 and this slow wave activity can then be used to derive noninvasive measures of cerebrovascular reactivity in a similar fashion to PRx, Mx, Sx, and ORx.

A derived index labelled as TOx was initially described as a moving correlation coefficient between 10 s averages of ABP and rSO_2 signals by Steiner *et al* in the context of sepsis.[166] The reference index used for this study was Mx and TOx showed a strong positive association. Both Mx and TOx react similarly to vasodilatation induced by carbon dioxide and both react to arterial hypotension.

Subsequently Zweifel *et al* assessed TOx in a study of patients with SAH and demonstrated good agreement with Mx when TOx was calculated against CPP or ABP.[162] In a subsequent study including 40 patients with closed head injuries, Zweifel *et al* focussed on an index derived from HbT.[167] Termed THx and derived as a measure of volume reactivity it was calculated as a moving correlation coefficient between ABP and HbT. As with other indices such as PRx, positive THx values indicate worse volume reactivity while smaller values (zero or negative) indicate better volume reactivity.

This work demonstrated that slow waves of CBV are represented by HbT signals in a manner similar to ICP. THx showed significant correlation with PRx. This is a consequence of the fact slow waves of intracranial blood volume, which are synchronous with the ICP slow waves that occur over 20 seconds to 3 minutes, are reflected by HbT. In addition, in around 50% of recordings contributing to THx calculation, the researchers were able to calculate optimal ABP (ABP_{OPT}) and optimal CPP (CPP_{OPT}). An ability to target an individual's optimal ABP without requiring invasive ICP monitoring would be a significant step for clinical care, although it is critical to note that it was not feasible to make that calculation in the other 50% of patients.

Summary of Near-Infrared Spectroscopy Across Clinical Settings

When clinicians first meet NIRS oximetry, the initial promise appears to be the resolution of multiple physiological variables into a single rSO_2 number that provides an insight into cerebral oxygenation. The reality is more complex.

While rSO_2 could be described as a percentage measure of the proportion of oxygenated Hb within a volume of sampled tissue, the actual contributors to that picture include the percentage contribution of both the arterial and venous blood volumes in the sampled tissue, along with Hb concentration, peripheral arterial oxygen saturation, oxygen consumption by the tissues and perfusion pressure which is itself influenced by ICP and the constant variation produced by autoregulation.

Across clinical settings such as cardiac surgery and carotid endarterectomy surgery, NIRS-derived rSO_2 appears to help identify those at risk of cerebral ischaemia, strokes and poor neurological outcomes. However, intervention seeking to normalize rSO_2 has been less successful in showing a meaningful difference in outcomes for patients.

In the setting of head injury, NIRS has been utilised as a screening tool to highlight the potential side of injury with a degree of sensitivity and specificity. Time spent under a threshold rSO_2 of 60% appears to be associated with patient mortality and at a similar threshold there was reasonable accuracy for predicting severe brain hypoxia but not moderate brain hypoxia.

There is still substantial work to be done to bridge the gap between observation of physiological changes that went unseen before this form of non-invasive cerebral oximetry was available and

providing clinical teams with critical information they can act on. Part of the issue may relate to the nature of analysis. An observation that rSO_2 is low does not precisely suggest to a clinician which of the contributing parameters would be best to address. With so many contributors to the displayed rSO_2 number, a different approach is needed.

Given that work to derive cerebrovascular reactivity indices from both rSO_2 and HbI highlights a need for monitoring over 30 minutes or more focussing on a single threshold cut off may not be an adequate aid for clinicians or patients. As described above, NIRS tissue oximetry does not provide a true absolute measure but a highly responsive trend. The key step may be to develop a means of providing useful indices of cerebrovascular reactivity on a shorter timescale than 30 minutes, or an approach to analysis that can link evolving trends to patient pathophysiology in a way that alerts clinicians to intervene. For patients, new approaches to monitoring need to be coupled with a meaningful prompt to action to make a difference to their future.

Specific Monitoring Challenges in the Prehospital Environment

These studies take place specifically in the prehospital environment. While patient care and monitoring can be challenging inside the walls of a hospital, the chaos of the clinical work environment before the patient reaches the hospital imposes major practical challenges for assessment and treatment. That these challenges occur at a time in close proximity to the initiating injury and during a period which may extend for more than an hour into the risk period for establishing secondary brain injuries makes it particularly worth focus.

The prehospital environment interferes with the application of all clinical skills. Undertaking a thorough patient history and examination ideally requires particular conditions. A patient free of

distractions, in a quiet and appropriately lit contained environment is required to facilitate full assessment. The prehospital environment rarely meets these specifications.

The patient who has recently suffered traumatic injuries is likely to be suffering distress and pain. Lighting conditions are highly variable, stretching from total darkness to bright sunlight. The auditory conditions are more likely to be chaotic than quiet. It is a highly changeable situation with containment and security never assured.

In this setting, monitoring becomes particularly valuable. Where the senses of the clinician are potentially overwhelmed by interference, effective monitoring can circumvent this issue. The cognitive load of undertaking patient care while also dealing with the safety and logistics problems of the prehospital environment creates a significant risk that key clinical changes might be missed. In this situation monitors with alarms to direct the clinician's attention to a critical evolving issue can be life-saving.

To the earlier list of desirable features of the ideal monitor of oxygenation and perfusion from Shephard *et al*, additional features must be added for the prehospital setting:

- It should be portable.
- It must be lightweight.
- It must be robust enough to withstand potential physical damage.
- It must perform in variable light conditions.
- Sensors must be practical for prehospital conditions such as patient movement.

Standard monitoring requirements for the prehospital and retrieval environment have been described by relevant professional bodies.[173] Monitoring of the critically ill patient requires

pulse oximetry with a plethysmographic waveform display, blood pressure measurement, electrocardiography and end-tidal carbon dioxide in patients with advanced airways in place in the form of either an endotracheal tube or supraglottic airway device. In the prehospital environment all of these monitoring methodologies may be somewhat compromised. In the context of TBI, the key physiological monitors are pulse oximetry and blood pressure, along with end-tidal capnography in the intubated patient.

Pulse Oximetry and the Prehospital Environment

Pulse oximetry was the first noninvasive monitor capable of providing information about patient oxygenation when the device was described in 1974.[174] After development it was rapidly adopted in a variety of clinical areas such as the perioperative environment to allow early notification of hypoxaemia. Despite this ability to allow early diagnosis and treatment of hypoxaemia, there is less evidence that applying pulse oximetry influences complication rates. Pedersen *et al*. were unable to find reliable evidence of improved anaesthetic outcomes with the use of pulse oximetry.[175]

In the prehospital setting pulse oximetry studies indicate that hypoxaemia, defined as SpO_2 less than 90%, is associated with poor clinical outcomes, particularly in TBI.[62,63] Although pulse oximetry has been incorporated into prehospital guidelines, evidence that this has altered patient outcomes is also lacking.[2] There is evidence that first responders of different clinical levels will institute oxygen therapy more often when pulse oximetry is available compared to when they rely on clinical assessment alone. The evidence that this changes clinical outcomes for patients is lacking.[176]

Modern pulse oximeters are another example of application of the modified Beer-Lambert law. The difference compared to NIRS oximetry is that pulse oximetry systems use only two wavelengths of light in the visible spectrum and generally position the emitters and detector across a tissue bed so that they are relying on transillumination.[177,178] Critically, pulse oximeters rely on a comparison between absorption behaviour during pulsatile vs non-pulsatile flow.

Particular issues for prehospital medicine arise from the design and validation of pulse oximetry. True validation of pulse oximetry values has been conducted only in volunteers. As a result, the lower the amount of haemoglobin saturated with oxygen, the less accurately this is reflected by pulse oximetry measurement, although accuracy appears to be acceptable in the prehospital setting where true peripheral oxygen saturation is 88% or above.[179]

Pulse oximeters may also produce incorrect readings in the setting of high levels of ambient light. When exposed to large amounts of ambient light, the measured values will tend to read towards 85% SpO_2.[178] In the prehospital environment this may be further complicated by variable light conditions. This may include variability in environmental light conditions or strobing produced by rotary wing aircraft.

Accurate readings also require a degree of pulsatile flow in the area the monitoring probe is applied. This means that anything compromising perfusion to the skin may influence the readings. This may be an issue in the setting of low cardiac output states, any case of vasoconstriction or in hypothermia.[177] Of note, in a perioperative setting pulse oximetry failure rate increased from 2.5% to 7.2% in patients who were critically unwell.[180] All of these situations are clinically relevant to the critically ill prehospital patient. Patient movement is an additional source of

potential artifacts which is not entirely eliminated by measures such as signal extraction in modern oximeters. This is only compounded by the prehospital reality of clinical care occurring through patient extrication, transfers and movement in vehicles.[181]

Blood Pressure Measurement and the Prehospital Environment

Similarly to prehospital hypoxia, the association between prehospital hypotension and worse patient outcome is well established and monitoring blood pressure and avoiding hypotension feature in TBI guidelines along with specific prehospital guidelines.[2,62,63,71]

There are two methods for blood pressure measurement in clinical use in the retrieval setting. The gold standard is intra-arterial blood pressure (IABP) monitoring via a pressure transducer connected to an intra-arterial catheter. Considerations including time to undertake insertion of the intra-arterial catheter and infection risk limit the widespread applicability of this technique in prehospital care.

Non-invasive blood pressure measurement is generally achieved by automated oscillometric devices. These devices automatically inflate a chosen blood pressure cuff to a value likely to be higher than the patient's systemic blood pressure. They then deflate in a stepwise fashion. Systolic blood pressure is recorded when oscillation in the blood pressure measured by the cuff is detected. The maximum oscillation in cuff pressure around a value is recorded as the mean arterial blood pressure, while loss of oscillation is marked as the diastolic blood pressure.

Oscillometric devices have well described issues with accuracy when compared to the gold standard or to manual recordings of blood pressure incorporating auscultation. In particular these

devices frequently significantly underestimate diastolic blood pressure.[182,183] This has led to the development of guidelines to describe appropriate clinical recording of blood pressure, particularly with oscillometric devices. [184,185]

Measurement methodology may have significant implications for patient management. Even in an ambulatory setting, adherence to the American Heart Association guidelines for blood pressure management compared to standard approach within a centre resulted in different recorded BP values.[186] This difference in measurement was then associated with alterations to blood pressure management. There is good reason to expect that differences in blood pressure measurements would have significant impacts on TBI management decisions given the importance of maintaining ABP targets.

Prehospital guidelines emphasise the need for regular measurement but not the method of measurement. Inaccuracy in BP measurements provided by noninvasive oscillometric techniques has been established in the aeromedical transport setting.[187] In the prehospital setting, it has historically been considered impractical to undertake IABP measurement. A prospective observational study has shown that out of hospital arterial catheterisation is feasible.[188] Success rates for arterial cannulation in this mixed patient population was 86% and the median time to cannulation after the decision to undertake the procedure was 12 minutes. However, only 11% of the patients (10 of 94) had a traumatic injury, with the majority being patients who had experienced cardiac arrest. Again, significant differences between blood pressure measurement were noted when compared to non-invasive measurements and IABP measurements led to a change in vasoactive treatment 79 times in 51 patients. This work suggests there may be a role for IABP measurement in the prehospital setting, particularly where the transit time to hospital is likely to be longer.

End-tidal Carbon Dioxide and the Prehospital Environment

End-tidal carbon dioxide monitoring is considered to be the standard of care in the monitoring of patients managed by physicians who have been intubated. Despite this its use has not always been universal amongst those undertaking airway management in the non-operative setting.[189]

Under normal physiologic conditions, end-tidal CO_2 partial pressure is close to arterial partial pressure of CO_2. Even varying levels of physiologic dead space seem to allow reasonable accuracy of measurements.[190] Monitoring of exhaled carbon dioxide is therefore an indirect measure of metabolism, circulation and ventilation.

End-tidal CO_2 monitoring is generally displayed with waveform capnography which plots CO_2 concentration against time and therefore provides a display profile that allows the clinician to infer additional information about the patient.[191] In the prehospital setting this requires an understanding that for this patient population there may be a significant difference between end-tidal CO_2 and arterial CO_2.[192] This should be taken into consideration when the patient is suffering from any condition which increases physiological dead space such as chest trauma or hypovolaemia related to blood loss.

The more profound implication for the application of capnography in prehospital patients is that it has most often been applied after endotracheal intubation and this procedure itself may be associated with worse patient outcomes unless undertaken by a highly specialised team. Cohort studies have shown a mixed picture when it comes to patient outcomes and prehospital paramedic intubation.[193–196] Intubation and ventilation also places a significant burden on the treating

team to ensure hyperventilation leading to hypocapnia is avoided as this is associated with worse patient outcomes.[197,198]

Summary of Challenges of Monitoring in the Prehospital Patient Monitoring

The prehospital environment imposes additional challenges for clinicians undertaking prehospital care at a time. The environment itself renders some forms of clinical assessment extremely difficult and practitioners are therefore even more dependent on monitoring to provide insights into patient condition. However that same environment makes monitoring more difficult and more prone to error and interference.

The combination of patient movement, pathophysiology leading to reduced peripheral perfusion and ambient light conditions interrupt pulse oximetry. Blood pressure measurement is significantly impacted by movement artifact and inaccuracies in oscillometric measurement. End-tidal capnography requires adding the risk to the patient of intubation in a non-ideal environment with mixed evidence as to whether patients experience the full potential benefit of that intervention. No monitoring methodology is easier in the prehospital setting than in the hospital setting.

This is highly relevant to the consideration of the role of NIRS-derived tissue oximetry in the prehospital setting where it has tremendous potential to provide early insights into cerebral oxygenation and perfusion. Any NIRS oximetry device needs to be lightweight and portable enough to make it to the incident scene but rugged enough to survive that setting once patient care commences. Information derived from monitoring will be threatened by the interruptions of patient movement and ambient light conditions.

The key question is whether it is possible to obtain enough monitoring signal for this physiological monitor to contribute meaningfully to clinical care or prognostication.

Chapter 3

A Study Protocol for Comprehensive Evaluation of Prehospital Near-Infrared Spectroscopy Monitoring

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Study protocol for the PHANTOM study: prehospital assessment of noninvasive tissue oximetry monitoring

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Abstract

Background: Traumatic brain injury is a major cause of mortality and morbidity worldwide. It can be worsened by secondary injury particularly with hypoxia or hypotension. Current prehospital guidelines emphasise regular measurement of peripheral oxygen saturation and blood pressure but there is no monitor in use to provide direct information relating to blood flow or oxygen delivery to the brain tissue. This prospective cohort study will assess the utility of near-infrared spectroscopy monitoring in prehospital medicine in demonstrating injury, pathophysiology and associations with long-term functional outcomes.

Methods/design: A prospective cohort study will be conducted in prehospital services where physician/paramedic teams respond rapidly to patients suffering significant traumatic injuries. A study observer accompanying the clinical team will apply non-invasive near-infrared spectroscopy tissue oximetry using a Nonin EQUANOX 7610 Regional Oximetry monitor (TM Nonin Medical, Inc.). This will be applied to patients with traumatic injuries less than 30 minutes old requiring transport. Measurements will be taken at two sites on the forehead and one on the forearm. Clinical teams will be blinded to all monitoring values. Near-infrared spectroscopy tissue oximetry parameters of oxyhaemoglobin %, deoxyhaemoglobin%, total tissue haemoglobin index and regional oxygen saturation will be recorded. Separate statistical analysis relating to time spent with cerebral regional oxygen saturation values < 45% and time series analysis will be performed to demonstrate associations with acute phase outcomes including injuries seen on cerebral imaging, and long-term functional outcomes measured by Glasgow Outcome Score and Extended Glasgow Outcome Score will then be undertaken.

Discussion: This prospective cohort study will demonstrate associations evident from the earliest stages of prehospital treatment between near-infrared spectroscopy tissue oximetry values and both acute and long-term outcomes of patients suffering traumatic injuries. This may provide the basis for future interventional studies utilising near-infrared spectroscopy tissue oximetry to guide prehospital trauma care.

Trial registration: This trial is registered with the Australian and New Zealand Clinical Trials Registry. The registration number is ACTRN12611001124921.

Keywords: Traumatic brain injury, Near-infrared spectroscopy, Prehospital

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Background

Traumatic brain injury (TBI) is a significant cause of death and severe disability [1]. Estimates suggest that long term costs of caring for people with moderate and severe TBI add $8.6 billion to health spending per year in Australia [2]. Despite advances in hospital care of patients with TBI, minimal improvements in outcome have been evident over the last twenty years [1].

In the setting of TBI, it is not only the initial injury that is responsible for patient outcome. After the initial insult, the brain is susceptible to further damage if normal physiologic conditions are not restored. Such insults include low blood pressure or hypoxia [3,4]. The primacy of hypoxia and hypotension in the debate has guided the development of consensus guidelines for prehospital management of patients with TBI with an emphasis on regular blood pressure measurements and checking oxygen saturations [5]. However, having this knowledge to guide monitoring care has not resulted in significant changes to patient outcomes.

Peripheral measurements such as non-invasive blood pressure and pulse oximetry remain relatively crude measurements distant to the tissue of most interest; the brain itself. Additional monitoring options that have become available in the hospital such as jugular venous bulb oximetry, direct tissue oximetry and intracranial pressure measurement are not appropriate to the prehospital environment [6-8]. In the New South Wales metropolitan setting, the time spent in the prehospital treatment phase before reaching a trauma centre averages over one hour [9]. This represents a significant period of vulnerable time where monitoring information relevant directly to cerebral tissue is absent.

Near-infrared spectroscopy (NIRS) tissue oximetry was first described in 1977 and is now used within hospitals [10]. It uses light in the near-infrared spectrum (700–1300 nm) and relies on the interaction of these wavelengths with tissue chromophores to derive information about oxygenated blood in the monitored region. Commercial devices use reflectance spectroscopy. The light is shone into tissues from an emitting light source within a self-adherent probe at the skin. Light entering the tissues interacts with chromophores, with the degree of absorption and scattering specific to the near-infrared wavelength employed. The fraction of transmitted light that returns to the surface is detected within the same probe, with a standard separation between the initial light source and the detector.

Utilising known characteristics of the interaction of particular near-infrared wavelengths with biological tissues allows the calculation of a number of parameters:

- Oxyhaemoglobin%, (HbO_2) a measure of haemoglobin carrying oxygen through the tissues;
- Deoxyhaemoglobin% (HbD), a measure of haemoglobin present but not carrying oxygen;
- Total tissue haemoglobin index (HbT) – an index (expressed in g/dL) corresponding with blood volume and flow within the sampled tissue; and,
- Regional oxygen saturation (StO_2%), providing a measure of the balance of oxygen delivery and utilisation in the tissue under the probe as it adjusts for the influence of chromophores other than oxy- and deoxyhaemoglobin as well as the adjustment for the proportional amounts of arterial and venous blood in the sampled area.

Recent monitors display improved accuracy and time resolution and are therefore spreading into a variety of clinical areas including detection of silent ischaemia in subarachnoid haemorrhage, coronary artery bypass grafting, aortic arch surgery, paediatric cardiac surgery and carotid endarterectomy [11-15].

NIRS oximetry has been utilised in head injury patients although application of the monitor has generally occurred hours after the initial injury. Early work with NIRS tissue oximetry has suggested that it may provide useful information in detecting intracranial haematomas and correlation with direct tissue oximetry. To date this work has been entirely hospital-based [16-19].

A further relatively recent development in the use of NIRS oximetry is the ability to use novel analysis techniques to assess dynamic factors such as cerebrovascular autoregulation. Various approaches such as coherence analysis of spectral waveforms and floating correlation analysis of moving value windows have been described in the assessment of vascular reactivity in subarachnoid haemorrhage, traumatic brain injury, paediatric cardiac surgery and extracorporeal membrane oxygenation [20-24]. Examples of this analysis rely on examination of the trends and patterns seen in the haemoglobin index (HbT) rather than analysis of absolute values of either HbT or rSO_2.

This study builds on earlier work demonstrating the possibility of obtaining NIRS oximetry monitoring values in the prehospital and transport environments [25]. It will assess the utility of prehospital NIRS oximetry in the monitoring of patients with TBI.

Study plan

The *hypothesis* is that NIRS tissue oximetry can provide direct real-time cerebral physiological data that provides an insight into rapidly developing brain pathology in TBI and its management, as well as early associations with long-term outcomes. Three aims will be delivered to achieve this:

1. To establish methods of analysing the NIRS tissue oximetry monitoring parameter time series that correspond with evolving pathology in the TBI.

2. To establish the association between NIRS tissue oximetry monitoring parameters and acute pathology in patients with TBI.
3. To establish the association between NIRS tissue oximetry monitoring parameters and the long-term recovery of patients after TBI, as assessed at follow-up to 12 months.

This research will therefore be conducted in a prehospital setting, providing early monitoring data in patients likely to have TBI with a plan for subsequent follow-up data collection to examine both acute and long-term outcomes. Novel analysis methods as featured in Aim 1 will provide better options for demonstrating the associations described in aims 2 and 3.

Study design and setting

This is a prospective cohort study.

This research will be conducted in a prehospital emergency medical service employing a physician-paramedic model of care to deliver rapid response trauma care and employing both rotary-wing and road transport modalities. The clinical team is capable of providing advanced life support, anaesthesia, intubation and ventilation, blood transfusion and peripheral haemorrhage control manoeuvres along with other critical care interventions at the scene of the accident or during patient transport.

Inclusion and exclusion criteria

All patients where patient contact is within 30 minutes of the injury and who are being transported to the trauma centre by the prehospital clinical team will be considered for inclusion. Exclusion criteria include:

- Patients < 1 year old and > 70 years old.
- Patients with pre-existing neurological disease or neurological trauma.
- Patients with no mechanism for trauma, (e.g. drowning, medical complaints);
- Patients with forehead haematomas or lacerations precluding NIRS probe application;
- Patients where follow-up consent is not later obtained from the patient or family.

Exclusion criteria may be apparent at the accident scene or may be applied upon the collection of additional information that reveals the patient meets exclusion criteria.

Monitor application

For the purposes of this research, NIRS cerebral oximetry will be applied by a trained researcher as soon as possible after arrival at the patient to ensure the clinical team are able to undertake their standard approach to care. The monitor employed will be a Nonin EQUANOX 7610 Regional Oximetry monitor (TM Nonin Medical, Inc.). This trained observer will apply monitoring probes bifrontally to the forehead of patients and to a peripheral reference site on the forearm (Figure 1). Monitoring will be commenced within a time frame of 30 minutes after the initial injury. The monitoring screen will only show that data capture is proceeding with warning signals if there are issues with sensor contact or signal quality. The EQUANOX 7610 monitor will continuously store the NIRS monitoring data. NIRS monitoring will cease on patient handover at the receiving hospital.

Data collection

Data collected by the research nurse, who will be blinded to NIRS monitoring information, will include patient demographics already recorded as a routine (available at the time of the injury) and via hospital follow-up. Trauma incident data including incident time and total prehospital duration will also be recorded in initial case documentation.

NIRS monitoring data

Each NIRS oximetry probe will continually produce 4 streams of data: StO_2; HbT; HbO_2; and HbD with values recorded every 4 seconds. Standard clinical monitoring will be recorded at the same time as the NIRS oximetry data captured by the EQUANOX device. This will include peripheral pulse oximetry, end-tidal capnography (where indicated for patient care), heart rate and non-invasive blood pressure and will be updated on the record every ten seconds. This general observations data will be time-matched to the NIRS oximetry monitoring

Figure 1 Cerebral oximetry probes applied to a volunteer during helicopter transport as part of feasibility testing.

data to allow direct comparisons of values in data analysis, particularly in the signals analysis related to Aim 1. Clinically relevant information such as any degree of prehospital hypoxia or hypotension will therefore be time-matched to the NIRS oximetry monitoring data.

Patient event and intervention marking

The data capture system for the NIRS oximetry monitor will also facilitate real-time marking of clinical events and interventions by the study observer. This will include real-time marking of bag-mask ventilation, cardiopulmonary resuscitation, anaesthesia with thiopentone, anaesthesia with ketamine, intubation, institution of mechanical ventilation, administration of vasopressor, transfusion, administration of hypertonic saline and seizure activity. Study observers will also have the ability to mark other potential events deemed clinically relevant. This will provide accurate information on interventions undertaken in a manner that is time-matched to the NIRS oximetry monitoring data. Event marking will be combined with NIRS oximetry monitoring data and general observations monitoring to allow reporting of standard interventions and care as previously described [26]. Patient general observations monitoring information and management and intervention details will be presented in conjunction with all outcome data.

Early phase outcome data

Patient outcome and follow-up data related to initial findings and hospital stay will be obtained from the hospital by the trial research nurse at a time beyond 30 days from the injury and include: (1) Injury Severity Score (ISS) and Abbreviated Injury Scores (AIS) for each body region [27,28]; (2) injuries identified on independent review of first cerebral imaging by computerised tomography (CT) or magnetic resonance imaging (MRI); (3) 24 hour and 30 day mortality; (4) survival to hospital discharge; and, (5) length of intensive care unit (ICU) stay including number of ventilator days.

Long-term outcomes

Follow-up by the research nurse will be undertaken via phone interview with the patient or appropriately identified relative as previously described [29] to assess and record (1) Glasgow Outcome Scale score (GOS) and Extended Glasgow Outcome Scale (EGOS) score at 6 and 12 months post injury [30]; (2) Disability Rating Scale (DRS) at 6 and 12 months post injury [31] and, (3) Care and Needs Scale (CANS) at 6 and 12 months post injury [32].

Power analysis

Pre-existing datasets showing the relationship between prehospital NIRS oximetry values and patient injury outcomes in the context of TBI are lacking. To answer Aim 1, a sample size of 242 subjects with severe TBI will provide 90% power to detect correlation of 0.22 or higher [33] in a 2-sided 0.05 level test of the null hypothesis of no correlation between NIRS cerebral oximetry values and admission Glasgow Coma Score (GCS) adjusting for 29 (approximately 12%) unsuccessful NIRS monitoring data collection attempts (25) in a time series based regression analysis. CareFlight's historical mission database indicates 1210 total recruits will be required to incorporate 242 subjects with severe TBI.

To address Aims 2 and 3, the same number of subjects will be enough to show an incidence of EGOS 4 at six months post-injury of 56% (95%CI 49% to 63%) and demonstrate a clinically important change in EGOS of 1 point associated with NIRS cerebral oximetry value at 80% power to detect a Cochrane-Armitage test for trend in EGOS groups (30% deceased, 20% poor neurological outcome and 50% good neurological outcome) at significance level of 0.05. The expected proportion of EGOS groups have been taken from the subject characteristics from the Head Injury Retrieval Trial [data under analysis] [29].

As for validation of the model for Aims 2 and 3, we will internally validate the models using bootstrapping methods on 1000 samples.

Subgroups for analysis and reporting

Some patients, particularly those with more severe injuries and those of a different age, are more likely to have monitor findings indicating strong associations with outcomes and are therefore of particular interest. Subgroup analysis will be undertaken on patients with severe TBI (first GCS ≤ 12 and Abbreviated Injury Score (Head) ≥ 3), severe traumatic injury (ISS > 15), and paediatric patients (age < 16 years).

Data analysis

Novel analysis methodology to address aim 1: establishing new analysis methods

A variety of approaches to signals analysis as commonly utilised in biomedical engineering fields will be undertaken. These will include (but not be limited to) time series analysis and pattern recognition and classification undertaken on all monitoring value streams (StO_2, HbT, HbO_2 and HbD) for each of the cerebral probes separately, and the peripheral reference probe. These may be matched to ancillary signals including peripheral oxygen saturation and electrocardiograph parameters (RR and QT intervals, RR variability). Comparison may also be made between NIRS oximetry probes. Control group

patients with traumatic injuries but no brain injury will be the reference group for analysis of "standard" signals analysis patterns comparisons.

Novel analysis methods applied to acute phase outcomes

Analyses undertaken in this way will be tested against the following changes seen on cerebral imaging: no intracranial pathology, intracerebral lesions (haemorrhage or contusion), subdural haematoma, extradural haematoma, traumatic subarachnoid haemorrhage and diffuse injury. Comparison to 24 hour and 30 day mortality will also be undertaken. Control group patients with traumatic injuries but no brain injury will provide data for analysis of "standard" signals analysis patterns.

Novel analysis methods applied to long-term outcomes

Analysis as described above will also be assessed against long-term outcomes as grouped by EGOS score at 6 and 12 months as described in the statistical analysis (EGOS < 2, 2–4 and 5–8).

Outcomes for aim 1

Exploration of a variety of signals analysis approaches to analyse NIRS cerebral oximetry is an explicit component of the study design. Establishment of useful approaches of this nature offer the greatest chance to develop real-time non-invasive monitoring that reflects the underlying pathology that is developing. This has implications not just for future management relevant to all prehospital practitioners but may inform better approaches to utilising NIRS cerebral oximetry in hospital care.

Statistical analysis for aim 2: associations of nirs tissue oximetry with acute phase outcomes

The area under the curve for cerebral oximetry value ≤ 45% (minutes x desaturation points ≤ 45%) will be used as an independent variable for statistical analyses as described previously [34]. Patients with one or more episodes of cerebral oximetry value ≤ 45% for 1 minute will be classified as experiencing a decline in cerebral oxygen saturation.

We will define 3 NIRS cerebral oximetry patient groups:

(1) NIRS 1 (cerebral oximetry values remain > 45% i.e. area under the curve = 0 min%).
(2) NIRS 2 (cerebral oximetry values ≤ 45% for > 0 min up to the median area under the curve for cerebral oximetry value ≤ 45% to be determined).
(3) NIRS 3 (cerebral oximetry values ≤ 45% for more than the median area under the curve for cerebral oximetry value ≤ 45% to be determined).

The total duration (minutes) of $StO_2 \leq 45\%$, longest duration (minutes) $StO_2 \leq 45\%$, minimum and average StO_2 will be derived for each patient. These variables will be compared between NIRS 1, NIRS 2 and NIRS 3 groups using Kruskal-Wallis analysis of variance to check the validity of this grouping.

A chi-square test will be used to assess the association between cerebral oximetry values by comparing patients in each of the above groups in their association with the following injury patterns on cerebral imaging: no intracranial pathology, intracerebral lesions present, subdural haematoma, extradural haematoma, traumatic subarachnoid haemorrhage and diffuse injury. The same analysis will also be repeated to establish associations with 24 hour and 30-day mortality and survival to discharge.

In the multivariate analysis, an ordinal logistic regression under a proportional odds model with NIRS 1 as the reference group will be used with the six types of injury on cerebral imaging listed above included as an independent variable after adjusting for ISS, age, sex and other covariates (mean arterial pressure, first recorded GCS, peripheral oximetry, end-tidal CO_2, HbT) in a stepwise fashion. A score test will be used to verify the proportional odds assumption in the final model. The unadjusted and adjusted odds ratios and 95% confidence intervals will be reported. Significance will be set at $P < 0.05$.

Outcomes for aim 2

This analysis will establish the associations between NIRS cerebral oximetry values and types of brain injury. This will underpin new approaches to interpretation of NIRS tissue oximetry values to provide real-time information corresponding with the development of pathology underlying the cerebral oximetry probes, be that swelling and oedema or acute development of blood collections.

Statistical analysis for aim 3: associations with long-term outcomes

Utilising the same groupings for NIRS tissue oximetry (NIRS 1 through 3), associations with EGOS (grouped into EGOS < 2, 2–4 and 5–8), GOS and CANS will be tested with the same multivariate analyses and ordinal logistic regression approach described above. This will include adjustment for ISS, age, sex and other covariates. For validation of the model for Aims 2 and 3, we will internally validate the models using bootstrapping methods on 1000 samples. All data analysis will be performed using SPSS version 21 and STATA 13.1 software (StataCorp, College Station, TX).

Outcomes for aim 3

This analysis will establish simple associations between NIRS cerebral oximetry values and the subsequent long-

term functional recovery of patients with TBI. This would potentially allow early identification of patients with more severe injuries to optimise early intervention and engagement of rehabilitation services.

Research ethics

This project has lead ethics approval from the Sydney Children's Hospital Network Human Research Ethics Committee (reference 11/SCHN/212). An initial waiver for consent to data collection has been provided as delays to patient care caused by an upfront process would be inappropriate. During the follow-up phase, consent will be obtained from the patient or, where more appropriate, a family member to undertake ongoing data collection and analysis. A Data Safety and Monitoring Committee has also been empanelled. This group will utilise reports from the investigators to confirm that there are no delays or alterations to patient care once the study is under way. Rigorous data security will be maintained for 15 years or, in the case of paediatric patients, until the subject reaches the age of 25.

Discussion

The ideal prehospital monitoring technology for the patient with TBI would be a non-invasive monitor that provides real-time information regarding conditions in the brain tissue. Appropriately validated this would provide the treating clinician as to what the organ needs at that moment to decrease the size of acute injuries and enhance patient recovery in the long term.

NIRS tissue oximetry may provide such an option. It is easy to apply without delay. In the hospital setting good sensitivity has already been demonstrated for detection of intracranial haematomas preoperatively when correlated with CT or MRI [16-18]. Correlation with invasive monitoring has shown mixed results. Increased length of time with an StO_2 below 60% has been associated with intracranial hypertension, decreased cerebral perfusion pressure and mortality in a small observational study [33]. In this study, monitoring was applied at the time of cerebral imaging, but this occurred anywhere up to twelve hours after the initial insult.

Research comparing regional oxygen saturation to direct, invasive brain tissue oxygen tension in 22 patients for the 16 hours after severe traumatic brain injury showed moderate accuracy in detecting severe brain hypoxia with area under curve on receiver-operating characteristic curve of 0.82 (with a likelihood ratio of a positive test of 5.3) but a poor ability to detect moderate hypoxia [19]. In this study patients had already passed the phase where they required resuscitation, and had all received neurosurgery. As a result many hours had passed and the subsequent monitoring and analysis is not reflective of early stage pathology.

The prehospital context is precisely about these early stages. Presently available research suggests there is good reason to be interested in cerebral tissue oximetry for this clinical setting, but cannot be considered as knowledge that can be directly transferred. This research will generate new evidence about the potential utility of NIRS tissue oximetry in the prehospital environment. It will be directly related to the prehospital treatment phase with the ability to include recording of general prehospital observations and patient interventions including transfusions and standardised reporting of prehospital airway management [26]. Many of the initial concerns relating to potential interference with cerebral tissue oximetry measurements, including varying venous and arterial compartments in the sampled tissue, oedema, bruising and jaundice have proven to be surmountable with probe placement and looking at monitoring values over time [35]. As obtaining monitoring values has been demonstrated to be feasible in the prehospital setting, there is no reason to believe that this technology cannot be employed in this new clinical context [25].

This study design will facilitate the acquisition of new knowledge directly relevant to prehospital medicine. The data analysis plan will explore associations with broad groupings of regional oxygen saturations as well as more dynamic measures of changing measurements over time through varying approaches to time series analysis. Moreover it will address both early and evolving pathophysiology by exploring associations with findings on cerebral imaging, as well as long-term functional outcomes that may be associated with early cerebral tissue oximetry values. Demonstrating such associations could both deepen our understanding of early pathophysiology of TBI, and provide the basis of future research where clinical interventions are guided by tissue oximetry values.

Abbreviations

TBI: Traumatic brain injury; NIRS: Near-infrared spectroscopy; HbO_2: Oxyhaemoglobin; HbD: Deoxyhaemoglobin; HbT: Total tissue haemoglobin index; StO_2: Regional oxygen saturation; ISS: Injury severity score; AIS: Abbreviated injury score; CT: Computerised tomography; MRI: Magnetic resonance imaging; ICU: Intensive Care Unit; GOS: Glasgow outcome score; EGOS: Extended Glasgow outcome score; DRS: Disability rating scale; CANS: Care and needs scale; GCS: Glasgow come score; CO_2: Carbon dioxide.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AW, AG and JS were involved in initial concept development, feasibility testing and study protocol development and review. NL and SR were involved in protocol development and planning of outcomes analysis, particularly time series analysis approaches. AL was involved in protocol development and planning of outcomes analysis, particularly statistics analysis. JE was involved in protocol development and manuscript preparation. All authors read and approved the final manuscript.

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Chapter 4

Analysis of Signal Capture in the Prehospital Environment

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ORIGINAL ARTICLE

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Near-infrared spectroscopy monitoring in a pre-hospital trauma patient cohort: An analysis of successful signal collection

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Background: Noninvasive monitoring of cerebral physiology could potentially guide pre-hospital management of patients with traumatic injuries. Near-infrared spectroscopy (NIRS) is one such modality but the consistency of monitoring performance remains unclear. This study assessed the proportion of successful signal collection during pre-hospital care.

Methods: As part of a prospective observational study, an independent study observer placed three sensors for a Nonin 7610 NIRS device; two on the forehead and one on the forearm. NIRS records were analysed for time of adequate monitoring signal in each sensor (>70% of total pre-hospital time). We also compared pre-hospital scene and transport times for patients with or without NIRS monitoring.

Results: Sixty-three patients with monitoring sensors applied were compared to 255 patients where no study observer was on board and 97 without NIRS monitoring for various reasons within the same time period. The proportion of pre-hospital time with successful monitoring (>70%) was 71.4% (45 of 63) for all three sensors, with at least two sensors functional in 90.4% (57 of 63). The median (interquartile range) scene time was 19 (11-23) minutes in patients with NIRS monitoring compared to 18 (11-27) minutes without NIRS monitoring (P = .570). There was no difference in the median (interquartile range) total pre-hospital time between patients with or without monitoring sensors (72 [59-89] versus 72 [59-80] minutes; P = .605).

Conclusions: In this pre-hospital observational feasibility study with dedicated personnel an acceptable proportion of measurement time was achieved in over 90% of monitored subjects. Addition of NIRS monitoring did not alter pre-hospital scene or transport times in this research setting.

1 | INTRODUCTION

A primary aim of managing critically injured patients is the maintenance of perfusion to vital organs, particularly the brain. Discussion of traumatic brain injury (TBI) management frequently focuses on hospital care but the pre-hospital phase, even in urban areas of Australia, is often more than one hour. Delivery of nutrients to the brain is no less vital during this period than during the hospital admission to prevent the deleterious effects of secondary brain injury.

TBI is a significant cause of morbidity and mortality with younger age groups most commonly affected. In TBI survivors, almost 50% have permanent deficits causing at least moderate disability.[1] Such disability can be present in up to 43% of patients up to 20 years after their injury.[1] With estimates that patients suffering TBI add $8.6 billion per year to the costs of health care in Australia, there is a clear rationale for pursuing optimal TBI management.[2]

Abbreviations: CRRH, CareFlight Rapid Response Helicopter; NIRS, near-infrared spectroscopy; TBI, traumatic brain injury.

Hospital TBI guidelines have recently been updated but current pre-hospital guidelines lag in their recommendations relating to monitoring, thresholds for blood pressure and perfusion management.[3] Guidelines of this nature are largely derived from registry data and are therefore based on uncontrolled cross sections of the population.[4,5] Even if hospital guidelines are extrapolated and a systolic blood pressure of 110 mm Hg is targeted, that target is not specific to the requirements of the individual patient or the needs of their cerebral tissue.[6] Similar issues apply to recommendations to maintain oxygen saturations above a critical threshold of 90%. If pre-hospital providers rely on these guidelines alone there is little ability to discriminate between groups in a way that tailors interventions or parameters. They provide only a single threshold in a heterogeneous population of patients. These guidelines cannot provide guidance on monitoring specific to cerebral tissue, for which pre-hospital options are limited.

Near-infrared spectroscopy (NIRS) is a technology first described in 1977 which has demonstrated more clinical utility in recent times.[7] Commercial devices utilize multiple emitters of light in the 700-1300 nm wavelength range. Reflectance spectroscopy combined with a knowledge of the absorption spectra for specific chromophores such as oxy- and deoxyhaemoglobin at those different emitted wavelengths allows the monitoring system to provide information relating to regional oxygen saturation, oxy- and deoxyhaemoglobin and an index of haemoglobin in the region of the sensor. This delivers additional information relevant to oxygenation, perfusion and nutrient delivery.[8]

Early evidence suggested that this monitoring technology may have value in detecting traumatic subdural haematoma.[9,10] As the technology provides information about perfusion and oxygenation of the tissue bed underlying the sensor, it has been used to define thresholds for safe perfusion during carotid endarterectomy, to provide information during cerebral aneurysm embolization, and in a variety of cardiac surgery settings including high-risk surgery, arch surgery and for monitoring during cardiopulmonary bypass.[11-15] Changes to cerebral oximetry values can be addressed by measures including increasing delivered oxygen, allowing carbon dioxide to rise to increase cerebral blood flow, use of agents to alter haemodynamics or transfusion.

This technical feasibility study was conducted as part of the Prehospital Assessment of Noninvasive Tissue Oximetry Monitoring Study (The PHANTOM Study) to determine if NIRS monitoring signals could be obtained in the majority of cases, and whether it interfered with clinical care.[16] The primary objective was to determine the proportion of successful monitoring, defined as more than 70% of the total monitored pre-hospital time. The secondary objective was to seek evidence of possible interference with clinical care by assessing the association between NIRS monitoring and total pre-hospital time.

Editorial Comment

Acute care of injured patients before arrival to hospital presents some monitoring challenges. Patients may be moved or transported in environments which can be hostile to sensitive medical devices. This study addressed feasibility of near-infrared spectroscopy as a monitor for cerebral oxygenation in this trauma patient pre-hospital setting. While promise was shown, some challenges were identified.

2 | METHODS

2.1 | Study setting

The PHANTOM study is a prospective observational study in a pre-hospital advanced clinical care setting with ethics committee approval via the Sydney Children's Hospitals network Human Research Ethics Committee (reference 11/SCHN/212).[16] As is allowed by the Australian National Health and Medical Research Council guidelines, an initial waiver of consent has been permitted for this research, with individuals subsequently approached to confirm consent at a time when they are not receiving medical care of a time critical nature.

The CareFlight Rapid Response Helicopter (CRRH) Service operates in the greater Sydney area covering a 100 km radius from a centrally located base providing access to a population of approximately 5 million people. The service is tasked by a central ambulance control room and incorporates a clinical team with an advanced level paramedic and critical care physician. This service provides advanced life support, anaesthesia, intubation and ventilation, thoracic decompression, blood transfusion and peripheral haemorrhage control manoeuvres along with other critical care interventions at the scene of the accident or during patient transport by helicopter or road vehicle.

For the purposes of the PHANTOM study, a trained study observer accompanies the clinical team to the incident. They are not available for all clinical shifts. All patients for transport with trauma as the reason for tasking and where patient contact is within 45 minutes of the injury are considered for inclusion in this study. The study period was from July 2014 to November 2016. No patient outcome data were examined for this study.

The exclusion criteria include:

- Patients <1 year old and >70 years old.
- Patients with pre-existing neurological disease or previous neurological trauma.
- Patients with no trauma mechanism.
- Patients with forehead haematomas or lacerations precluding sensor application.
- Patients who died before sensor application

Exclusion criteria are particularly aimed at excluding those likely to have confounding conditions (eg upper age limit, neurological disease, or non-trauma conditions) and those where logistics preclude reliable monitoring (lower age limits and forehead injuries). Exclusion criteria may be apparent at the accident scene. Some patients may be excluded from analysis if subsequent information indicates that the subject meets the exclusion criteria.

2.2 | Monitor application

The study observer applies NIRS oximetry utilizing a Nonin EQUANOX 7610 Regional Oximetry monitor (TM Nonin Medical, Inc) as soon as possible after arrival at the patient. Adhesive sensors are applied bi-frontally to the forehead of patients and to a peripheral reference site on the forearm to allow comparison of signal in different vascular beds as part of potential autoregulation assessment.[17] This results in three sensors gathering information on oxy- and deoxyhaemoglobin, regional saturation and haemoglobin index. The monitoring system indicates only that data capture is proceeding with alarm systems indicating loss of sensor contact or issues with data acquisition. The clinical team is not involved with the application of the monitoring sensors, maintenance of sensor contact, or marking of the NIRS oximetry record with clinical events.

2.3 | Data collection

Data were extracted from the central study database and by examination of the individual de-identified NIRS oximetry record indicating whether data were being captured by the monitor. The total monitoring time was defined as the time from commencement of NIRS monitoring to the time of arrival in triage. The proportion of total time for which measurements were successfully obtained were then calculated for each individual sensor for each patient. The primary endpoint was successful NIRS monitoring in at least two sensors for more 70% of total pre-hospital time. This would provide a reasonable expectation of clinically useful data.[16]

The secondary endpoints were scene time and pre-hospital time. Time of incident (in minutes) is recorded as the time of the first key stroke on a computer as the emergency call is logged. Time on scene (in minutes) is defined as the time from the moment the clinical team makes first contact with the patient, to the timepoint when transport towards the hospital commences. Total pre-hospital time (in minutes) is defined as the time from recorded first key stroke to the time of arrival at hospital triage. These times were extracted for subjects where the clinical team made first contact less than 45 minutes from the time of injury.

2.4 | Data analysis

Normality of the data was assessed visually and using the Shapiro-Wilk's test. Descriptive data are reported as frequencies, mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Missing data were checked and imputed to preserve power using the most common value for categorical variables or median for continuous variables (according to patient group defined below) if there were less than 20% missing data. To assess possible selection bias, a Kruskal–Wallis analysis of variance test was used to examine the association between age and study participants in Group 1 (with NIRS monitoring), Group 2 (no NIRS monitoring) and Group 3 (without study observer on board). Likewise, a chi square test was used to examine the association between gender and study participants in the three groups. We estimated the proportion of patients with successful monitoring over 70% of the total time and report the associated Wilson 95% confidence intervals. A Mann–Whitney U test was performed to compare the scene and total pre-hospital times between patients with and without NIRS monitoring. The same analyses were repeated in the 53 patients who had NIRS monitoring and met the inclusion criteria (sensitivity analysis) to assess how robust the findings were. The level of significance was set at two-sided $P < .05$. Statistical tests were performed using SPSS version 25.0 software (IBM Corp, Armonk, NY).

3 | RESULTS

Of the 415 patients screened for eligibility, 255 did not have a study observer available for NIRS monitoring, and another 97 patients did not have NIRS monitoring for reasons given in Figure 1. A comparison of patient characteristics by NIRS monitoring groups is shown

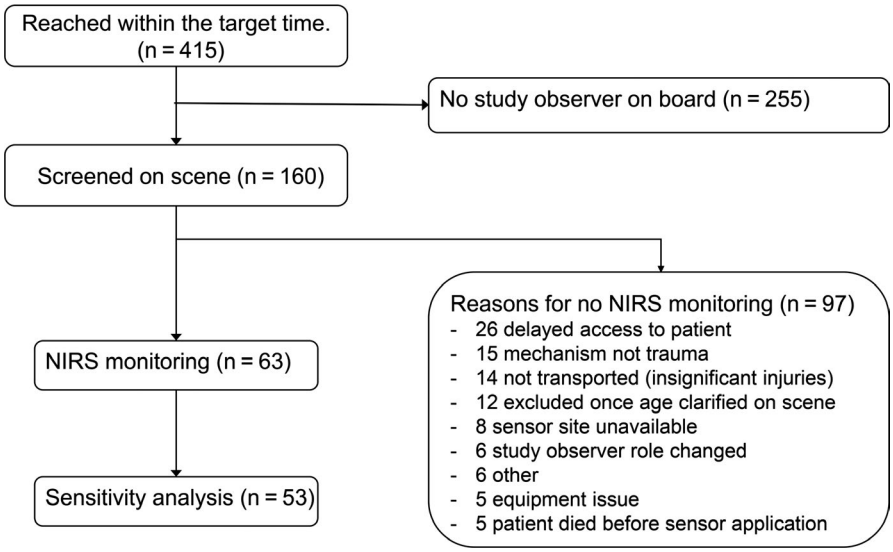

FIGURE 1 Patient flow diagram

in Table 1 with only the mechanism of injury different between the three groups (*P* = .025). In the sensitivity analysis, 10 patients with NIRS monitoring data were excluded due to age exclusion (n = 4), not transported by the clinical team (n = 3), burns (n = 2) and no mechanism of trauma (n = 1).

For the primary endpoint (n = 63), the median (IQR) percentage of pre-hospital time monitored in at least two functional sensors (>70%) was 91% (76%-95%) (Figure 2). The median (IQR) sensors exceeding target monitoring time of 70% was 3 (2-3). All three sensors were functional in 45 of 63 (71.4%, 95% CI: 59.3%-81.1%) patients (Table 2). In the sensitivity analysis (n = 53), the number of sensors achieving target monitoring time was similar, with three, two and one sensors achieving over 70% target monitoring time in 39 (73.6%), 9 (17.0%) and 5 (9.4%) patients respectively. The proportion (95% CI) of patients with two or three sensors (>70% of total time) was 90.6% (79.8%-95.9%); with all three sensors, the proportion (95% CI) was 73.6% (60.4%-83.6%).

For time spent at the scene, there was no difference between the three patient groups (Table 1); patients with or without NIRS monitoring also had similar scene times (*P* = .570). In the sensitivity analysis, the median (IQR) scene time for those with sensors applied who met the inclusion criteria (n = 53) was 19 (13-23) minutes,

TABLE 1 Patient characteristics by NIRS monitoring groups

	NIRS group (n = 63)	No NIRS group (n = 97)	No study observer group (n = 255)	*P* value
Median (IQR) age, years	40 (22-52)	29 (15-52)	32 (16-52)	.312
Sex, Male (%)	44 (69.8)	69 (71.1)	173 (67.8)	.825
Mechanism of injury (%)				
Motor vehicle accident	13 (20.6)	28 (28.9)	49 (19.2)	.025
Motorbike accident	13 (20.6)	7 (7.2)	32 (12.5)	
Pedal cyclist	3 (4.8)	6 (6.2)	10 (3.9)	
Pedestrians	7 (11.1)	11 (11.3)	41 (16.1)	
Sports/Horse riding	12 (19.0)	4 (4.1)	29 (11.3)	
Falls	7 (11.1)	9 (9.3)	37 (14.5)	
Burns	2 (3.2)	9 (9.3)	9 (3.5)	
Assault	2 (3.2)	3 (4.3)	7 (2.7)	
Other	4 (6.3)	15 (15.5)	32 (12.5)	
Initial Injury Severity Score (%)				
>15	19 (30.2)	32 (33.0)	76 (29.8)	.156
≤15	43 (68.3)	54 (55.7)	162 (63.5)	
Not applicable/ Unknown	1 (1.6)	11 (11.3)	17 (6.7)	
Median (IQR) first Glasgow Coma Score	15 (14-15)	15 (12-15)	15 (11-15)	.564
Mode of transportation (%)				
Road with medical escort	35 (55.6)	48 (49.5)	123 (48.2)	.099
Helicopter with medical escort	25 (39.7)	28 (28.9)	92 (36.1)	
Ground ambulance without medical escort	3 (4.8)	15 (15.5)	24 (9.4)	
Other/Unknown	0 (0.0)	6 (6.2)	16 (6.3)	
Median (IQR) time spent at scene, min	19 (11-23)	18 (11-27)	18 (12-27)	.828
Median (IQR) total pre-hospital time, min	72 (59-89)	72 (59-80)	70 (58-82)	.680

Abbreviations: IQR, interquartile range; NIRS, near-infrared spectroscopy

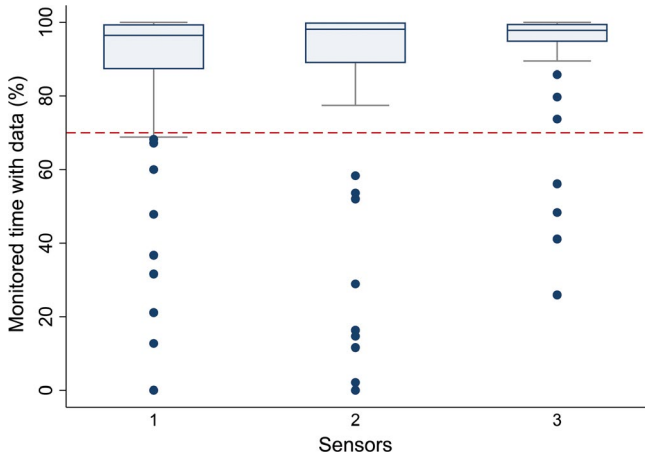

FIGURE 2 Percentage of monitored time with data by sensor in 63 patients. The boxplots show the median, 25th and 75th percentiles; upper and lower whiskers are 1.5*interquartile range. Reference line is the clinical acceptable target time of 70% determined a priori [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Proportions of monitoring time

Number of sensors achieving monitoring >70% of total time	Number of cases (% of total)
Three sensors	45 (71.4%)
Two sensors	12 (19%)
Forehead sensors only	3
One forehead/One peripheral	9
One sensor	5 (7.9%)
Zero sensors	1 (1.6%)

with no difference between patients with and without NIRS monitoring (P = .867). For total pre-hospital time, there was no difference between the three patient groups (Table 1); patients with or without NIRS monitoring also had similar total pre-hospital time (P = .605). In the sensitivity analysis, the median (IQR) total pre-hospital time for those with sensors applied and met the inclusion criteria (n = 53) was 77 (60 to 91) minutes, with no difference compared to patients without NIRS monitoring (P = .333).

4 | DISCUSSION

4.1 | Key findings

This preliminary feasibility study with dedicated personnel demonstrates that the key criteria of capturing information without delaying definitive care can be met in this context. We have defined a pragmatic cut-off point of 70% of the total monitoring period producing data capture. This is based on assessment of the proportion of successful monitoring from our other monitors used in pre-hospital care prior to commencement of this study. Having less than 70% monitoring information available would compromise any ability to demonstrate meaningful associations between NIRS monitoring parameters and patient outcomes. However, setting a level of cut-off so high that it does not reflect clinical practice would make any findings irrelevant to real-world pre-hospital medicine. In this interim analysis we have been able to demonstrate that all three sensors achieved adequate data capture in 71.4% of cases. Consistent performance in two of the three sensors should also allow some data analysis. With an additional 19% of cases displaying adequate data capture in two sensors, the overall proportion of subjects where monitoring was present in at least two sensors for more than 70% of the pre-hospital time was 90.6% in our series. Caution is warranted given the imprecision of the 95% confidence intervals in each of the two and three sensor groups. Nevertheless, the sensitivity analyses indicate that the overall results were robust to the strict a priori inclusion criteria.

As a secondary analysis, we also assessed the effect of investigating this technology on timely clinical care. Exploring the role of NIRS should not delay arrival at an appropriate trauma centre. Definitively proving delays on scene result in poorer patient outcomes is challenging and relies principally on observational studies. However, all pre-hospital care systems in first world settings expedite patient transport to an appropriate destination. This study indicates that in this pre-hospital feasibility study with a dedicated study observer managing the monitor, progress from the accident scene to triage in the emergency department is not changed.

4.2 | Feasibility of NIRS oximetry for clinical application in the pre-hospital setting

All monitoring modalities are challenged by the pre-hospital environment. Combinations of patient movement and the uncontrolled environment lead to frequent signal interruptions. For modalities relying on reflectance spectroscopy it is likely that ambient light is also a significant potential source of interference.

This study provides pragmatic reassurance that some technical limitations that might have affected NIRS oximetry in the field can be overcome. Although we have previously evaluated this in volunteers, this report extends this demonstration of feasibility of an absolute oximetry device in to the real world of pre-hospital trauma care.[18] Coupled with feasibility evidence in out-of-hospital cardiac arrest management, the promise of NIRS oximetry is still evident, though these reports have not focussed as extensively on the proportion of successful monitoring and often rely on a single NIRS sensor.[19-21] With extracranial contamination and ambient light in an operating theatre environment previously highlighted as potential issues, the demonstration that outdoor ambient light does not preclude monitoring is reassuring.[22,23]

The goal of NIRS monitoring should be to provide information that responds accurately enough to evolving changes in physiology to allow clinicians to make meaningful changes to their care and produce better patient outcomes. This relies on a consistent monitoring signal. Our research model utilized an individual solely dedicated to managing the monitoring but there remained gaps in signal acquisition. The study observer manages application of sensors and ensures continuous data

capture. In this research context this is a safeguard to ensure the clinical team is not distracted from patient care. However, both consistency of signal capture and pre-hospital times may be different where the clinical team are also required to manage the monitor.

Simpler NIRS-based technologies have shown variable results in detecting changes associated with pathology, with reports of good sensitivity from some authors.[9] However, recent feasibility studies in a pre-hospital HEMS setting showed high false-positive rates for haematoma detection.[24] A recent pilot study assessing technical feasibility in patients requiring pre-hospital anaesthesia showed that almost all (29/31) patients had successful NIRS monitoring signals from anaesthesia induction to hospital arrival.[25] Promising in-hospital uses in the setting of brain injury have been dependent on consistent signals coupled with multiple invasive measurements which are not currently available in pre-hospital care.[26,27]

Explorations of use in out-of-hospital cardiac arrest management have not relied on such consistent signals, but rather have focussed on changes in oximetry and their association with return of spontaneous circulation.[20,21] However, it is hardly surprising that a patient receiving protocolized arrest management that results in return of spontaneous circulation would demonstrate an increase in tissue oxygenation. While of interest, this is unlikely to result in meaningful changes in clinical care.

Ideal pre-hospital monitoring provides access to useful information that allows individualized care. Providing early evidence of evolving changes such as decrease in oxygen delivery, decreased cerebral blood flow, developing haematoma, anaemia or loss of cerebral autoregulation may be possible with this technology if reliable signal capture can be achieved. This would allow clinicians to intervene to increase oxygen delivery, provide sedation to decrease cerebral oxygen consumption, manipulate carbon dioxide to alter cerebral blood flow and commence red cell transfusion where appropriate. Blood pressure targets could be guided by cerebral tissue requirements and a nuanced understanding of whether autoregulation is intact rather than simplistically applying the same targets in all patients.

There is some in-hospital research after out-of-hospital cardiac arrest (OHCA) that hints at this potential for individualized care guided by cerebral NIRS oximetry. There is the potential to detect disturbed cerebral autoregulation in these patients.[28] Altered autoregulation in the first 24 hours was associated with worse patient outcomes (OR 4.62, 95% CI: 1.06-20.06) and time spent below an optimal mean arterial pressure defined for these patients was negatively associated with survival (OR 0.97, 95% CI: 0.96-0.99).[28] More recent work demonstrates that it is possible to target high normal arterial carbon dioxide and moderate hyperoxia and observe higher cerebral oxygen saturation.[29] However, this produced no change in detected markers of hypoxic brain injury.[29]

Clinicians working in pre-hospital settings should therefore interpret findings around the pre-hospital utility of NIRS oximetry with caution. Associations with changes in oximetry alone do not necessarily offer a true understanding of underlying changes in pathophysiology that might allow tailored interventions. Patterns in oximetry changes indicating evolving pathology may be hard to analyse when unpredictable gaps in the data are still an issue. Our findings in this feasibility study may indicate that further advances in the engineering of NIRS oximetry monitors that eliminate interruptions to signal acquisition may be required before its true potential can be realized.

4.3 | Study limitations

Logistics of our observational study dictated that study observers are only intermittently available. There was, however, little or no evidence of selection bias in the application of NIRS monitoring as suggested by the lack of any difference in age, gender, initial Glasgow Coma Score, Injury Severity Score and mode of transport distributions, except mechanism of injury, between the three patient groups. Nonetheless, the sensitivity analyses suggest that our results are robust.

5 | CONCLUSIONS

In this preliminary feasibility study data capture by NIRS oximetry in the pre-hospital setting was successful at a level consistent with pragmatic use of monitoring in this setting. There remain significant interruptions to data capture with NIRS oximetry. It remains unclear whether these interruptions would adversely affect clinical interpretation of those monitoring outputs. The addition of pre-hospital NIRS oximetry did not increase scene or pre-hospital times in this technical feasibility study.

CONFLICT OF INTERESTS

The authors have no financial or non-financial competing interests to declare.

AUTHORS' CONTRIBUTIONS

AW was responsible for study design, data collection and analysis, manuscript preparation and revision and submission of the manuscript. EP was responsible for data collection and revision of the manuscript. AG was responsible for study design, data collection and manuscript preparation and revision. AL was responsible for study design, analysis of collected data and manuscript preparation and revision.

DATA AVAILABILITY STATEMENT

The datasets generated and analysed during this study are available from the corresponding author on reasonable request, allowing for the need to confirm this release with the ethics committee.

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Chapter 5

Prehospital Cerebral Oximetry and Association with Patient Outcomes

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Association between prehospital cerebral oximetry measured by near-infrared spectroscopy and patient outcomes: a pilot study

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Title: Association between prehospital cerebral oximetry measured by near-infrared spectroscopy and patient outcomes: a pilot study

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Abstract:
Background
Brain injury is a major cause of morbidity and mortality arising from traumatic injuries. Advances in neurological multimodality monitoring have not been feasible in the prehospital environment. Cerebral oximetry utilising near-infrared spectroscopy offers a noninvasive method of measuring cerebral physiology.

Aim: This pilot study aims to explore associations between NIRS tissue oximetry monitoring parameters and patient outcomes.

Methods:
A prospective observational cohort study was conducted in patients with traumatic injuries in the setting of an advanced prehospital emergency medical services utilising the Nonin EQUANOX 7610 monitor. Patient outcomes included 24-hour and 30-day mortality, injuries on cerebral imaging, and 6-month and 12-month functional outcome measured by Glasgow Outcome Scale Extended (GOSE). Abnormal cerebral oximetry was defined as $rSO_2 \leq 45\%$ for > 1 minute. Subgroups for analysis included patients with severe traumatic injuries, severe traumatic brain injuries and paediatric patients.

Results: 79 patients were included in the final analysis with 14 of these subjects in the abnormal NIRS group. There was no evident association between abnormal NIRS and patient long-term functional outcome, patient mortality, abnormal CT or brain injury deaths.

Conclusion: There was no association demonstrated between rSO_2 and either short-term or long-term patient outcomes. NIRS oximetry devices require improvements before further dedicated prehospital research.

Introduction:
Traumatic brain injury (TBI) remains a major contributor to the morbidity and mortality arising from traumatic injuries globally. The global associated healthcare costs have been estimated as being as high as $US400 billion annually.[1–3]

Reducing the burden of TBI for society requires public health measures to reduce accident rates and early intervention and targeted therapy to reduce the secondary injury that worsens brain damage.

In hospital settings advances have been made in multimodality monitoring along with interventions targeting optimal cerebral perfusion pressure or limitation of damage created by intracranial hypertension.[4–6] Those requiring invasive pressure measurement are not available in the prehospital phase with less robust evidence to guide clinical care and fewer options for clinicians to make a difference to patient trajectory. Suggestions are limited to influencing oxygenation and targeting blood pressures that match a population mean.[7] However, prehospital care may be the phase where early provision of optimal physiological conditions for the injured brain could produce more profound outcome improvements for patients.

This landscape creates substantial interest in non-invasive options to acquire information about the micro-environment of the key tissue of interest – the brain. Near-infrared spectroscopy utilises the characteristic absorption spectra of light in the 750-810 nm wavelength range to provide a measurement of oxygenation of tissue underlying the sensor.[8] This technology offers the potential to provide information relating directly to cerebral tissue itself. This might facilitate treatment approaches targeting optimal physiological conditions to protect the injured brain from further damage.

There has already been some work done to explore the potential additive information provided by NIRS oximetry in the setting of prehospital anaesthesia, intracranial haematoma detection and in out-of-hospital cardiac arrest.[9–11] In this prospective pilot study, we sought to explore associations between NIRS tissue oximetry monitoring parameters and short-term and long-term patient outcomes.

Methods:
This prospective cohort study was approved by the Sydney Children's Hospital Network Human Research Ethics Committee (reference 11/SCHN/212). An initial waiver for consent to data collection was provided. Consent was subsequently affirmed during follow-up from either the subject themselves or, where more appropriate, a family member.

This study was undertaken at CareFlight, Sydney, Australia, an organisation providing advanced Emergency Medical Services utilising a physician-paramedic team. The service delivers rapid response trauma care via rotary-wing dispatch to the incident scene and both rotary-wing and road transport to hospital. Tasking to incidents is managed centrally via a separate dispatch system. The clinical team can undertake patient assessment incorporating point-of-care ultrasound and deliver advanced life support, anaesthesia, intubation and ventilation, blood product transfusion and other critical care interventions at the scene of the incident or during patient transport.

All patients where patient contact was within 45 minutes of the injury and who were being transported to the trauma centre by the clinical team were considered for inclusion during the period of the study when a study observer was available. Exclusion criteria were:

- Patients < 1 year old or > 70 years old;
- Patients with pre-existing neurological disease or neurological trauma;
- Patients with no trauma mechanism (e.g. drowning, medical complaints);
- Patients with forehead haematomas or lacerations precluding sensor application;
- Patients where follow-up consent was not obtained.

Exclusion criteria could be applied where apparent at the scene or upon collection of information revealing that the patient met exclusion criteria.

After the initial observational study protocol development recruitment dispatch parameters for CareFlight were altered by the central tasking authority.[12] This resulted in a substantial decrease in anticipated recruitment rates. After careful consideration of the parameters considered in calculation of the sample size as per the original protocol study recruitment was paused after proceeding from 6th July 2014 to 4th November 2018 and the analysis was treated as a pilot study.

The NIRS oximetry monitor utilised for this study was a Nonin EQUANOX 7610 Regional Oximetry monitor (TM Nonin Medical, Inc.). A trained researcher who was an addition to, and distinct from, the clinical team members applied monitor sensors as soon as possible after patient contact. This study researcher was responsible for continuing to assess and maintain adequacy of sensor contact and data capture throughout clinical care until patient handover at the receiving hospital. The clinical team were blinded from all oximetry values with the monitoring screen displaying only presence or absence of oximetry signal.

Regional oximetry sensors were applied to the right and left frontal regions of the head. An additional sensor was placed on the left volar forearm to assess a peripheral vascular bed. Each sensor recorded a value every 4 seconds for regional tissue oxygen saturation (rSO_2), total haemoglobin index (THb), oxyhaemoglobin (HbO_2) and deoxyhaemoglobin (HbD). Standard clinical monitoring including heart rate (HR), peripheral oxygen saturation (SpO_2), non-invasive blood pressure (BP) and end-tidal capnography ($EtCO_2$) (where appropriate for patient care) was captured to the record every 10 seconds.

Patient demographic data was obtained as part of the routine information available at the time of injury and via hospital follow-up. Incident data including incident time and total prehospital duration was obtained as part of standard clinical case documentation.

Hospital-based outcome data was collected by direct review of patient records and trauma databases at receiving hospitals. This included Injury Severity Score (ISS) and Abbreviated Injury Scores (AIS) for each body region, injuries identified on independent review of first and subsequent cerebral imaging by computerized tomography (CT) or magnetic resonance imaging (MRI), 24-hour and 30-day mortality, survival to hospital discharge and length of intensive care unit (ICU) stay including number of ventilator days.

Long-term outcome data was obtained by follow-up phone interview with the patient or appropriately identified relative as previously undertaken by this team.[13] This follow-up incorporated assessment and documentation of Glasgow Outcome Scale score (GOS) and Extended Glasgow Outcome Scale (EGOS) at 6- and 12-months post-injury, Disability Rating Scale (DRS) at 6- and 12-months post-injury, Care and Needs Scale (CANS) at 6- and 12-months post-injury and SF-10 for patients < 16 years of age at 6- and 12-months post-injury.

Abnormal NIRS cerebral oximetry was defined as $rSO_2 \leq 45\%$ for ≥ 1 minute as per the protocol first established in preparation of this study. A priori exposure subgroups evaluated included:

- Severe TBI (first GCS $\leq$ 12 and AIS (Head) $\geq$ 3).
- Severe traumatic injury (ISS > 15).
- Paediatric patients (age < 16 years).

Data Analysis
Complete case analysis was used. Descriptive data were reported as mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate after checking data for normality using the Shapiro-Wilk's test. Proportions (%) were reported for categorical data. Differences between NIRS groups were examined using chi-square tests, Student's t-tests or Mann-Whitney U tests as appropriate. Relative risks and associated 95% confidence intervals (95% CI) were estimated, with a 0.5 addition to all cells in the contingency tables to overcome zero counts in one or more cells.

The primary outcome was Glasgow Coma Score Extended (GOSE). We dichotomized GOSE as poor recovery (<5) and good recovery (≥5) for the generalized estimating equation (GEE) analysis using the modified Poisson regression model with robust estimator of variance, adjusting for severe Abbreviated Injury Scale Head and Neck (≥ 3) to obtain the relative risk associated with NIRS groups.[14] The model was based on a directed acyclic graph approach drawn before data-analysis after considering the observed numbers of patients available for the study. The model discrimination (validity) and calibration (reliability) properties were assessed using an area under the receiver operating characteristic curve (AUROC) and drawing a calibration belt to assess the agreement between observed and expected probabilities. Subgroup analyses were performed to assess the association between poor recovery (GOSE<5) with severe TBI, severe traumatic injury and paediatric subpopulations. Statistical analyses were performed using SPSS version 27.0 (IBM Corp, Armonk, NY) and Stata 18.0 (StataCorp, College Station, TX). Level of significance was set at $P<0.05$.

RESULTS

Of the 813 patients with injuries between 6th July 2014 to 4th November 2018, 79 were in the final analysis after applying the exclusion criteria (*Figure 1*).

NIRS characteristics

There were 49,625, 50,436 and 50,882 rSO_2 observations using Channels 1 (left forehead), 2 (right forehead) and 3 (volar forearm) respectively. The mean (SD) rSO_2 from channels 1, 2 and 3 were 77 (11)%, 79 (9)% and 70 (14)% respectively. The mean (SD) duration of monitoring using Channels 1, 2 and 3 were 47(20), 47(21) and 46(21) minutes respectively.

Fourteen (17.7%, 95% CI: 10.0% to 27.9%) of 79 patients had abnormal cerebral NIRS. Ten patients had abnormal NIRS from Channel 1, one from Channel 2 and the remaining three had abnormal NIRS monitoring from both Channels 1 and 2. The mean (SD) rSO_2 in the left forehead (Channel 1) of abnormal NIRS patients [65 (13)%] was lower than those in the patients with normal NIRS [79 (9)%] (mean difference -15%, 95% CI: -22% to -7%; P=0.001). Similarly, the mean (SD) rSO_2 in the right forehead (Channel 2) in patients in the abnormal NIRS group [74 (8)%] was lower than those in the normal NIRS group [80 (9)%] (mean difference -6%, 95% CI: -11% to 0%; P=0.035). However, the mean (SD) rSO_2 in the left volar forearm (Channel 3) in patients with abnormal cerebral NIRS [65 (17)%] was not lower than those with normal NIRS [71 (13)%] (mean difference -6%, 95% CI: -14% to 2%; P=0.167).

Six (7.6%) patients died within 30 days with brain injuries; two patients died within 24 hours, and the remaining four patients died within a week after injury. No further deaths during the 12 months of follow-up occurred after hospital discharge. None of the paediatric patients died during the 12 months of follow-up. The relative risk (95%CI) of death associated with abnormal NIRS was not significant at 24 (4.64 (95% CI: 0.31-69.85)), 30 days(2.32 (95% CI: 0.47-11.45)), 6 months (2.29 (95% CI: 0.46-11.27)) and 12 months post injury (2.14 (95% CI: 0.43-10.56)).

Prehospital phase characteristics

The prehospital characteristics of the study population by NIRS groups are shown in *Table 1*.

Hospital phase characteristics

The hospital characteristics of the study population by NIRS groups are shown in *Table 2*.
Sixty patients underwent CT scans. Of the 60 first CT scans, 49 (81.7%) were the worst cerebral imaging for that patient. There was no difference in the distribution of first CT and worst CT Marshall scores by NIRS groups (*Table 3*). However, there was a strong association between first and worst Marshall scores with hospital mortality (*Table 3*).

There was no difference in the proportion of brain injury deaths between abnormal NIRS (14.3%) and normal NIRS (6.2%) groups (P=0.287). Compared to patient without severe traumatic brain injuries, those with severe traumatic brain injuries were likely to die within 24 hours (RR 7.00, 95% CI: 4.05 to 12.10) and within 30 days (RR: 10.43, 95% CI: 5.16 to 21.09).

6-12 months outcomes

Glasgow Coma Outcome Scale Extended (Primary outcome)

There was no difference in GOSE distribution between NIRS groups in the pre-injury phase (P=0.155), at 6 months post-injury (P=0.342) or at 12 months post-injury (P=0.658) [*Figure 2A].* In the GEE analysis, there was no NIRS group (P=0.651), time (P=0.530) or group*time interaction

(P=0.206) after adjusting for severe head AIS. The adjusted relative risk of poor recovery associated with NIRS are shown in *Table 4*. The model had excellent discrimination and adequate calibration.

The GOSE distribution between severe TBI groups was not different at the pre-injury phase (P=0.891) but it was significantly different at 6 months post-injury (P<0.001) and at 12 months post-injury (P<0.001) as shown in *Figure 2B*. After adjusting for severe head AIS, there was a severe TBI group effect (P=0.005) but no time (P=0.724) or group*time interaction (P=0.724). The adjusted relative risk of poor recovery associated with severe TBI are shown in *Table 4*. The model had excellent discrimination and adequate calibration.

The GOSE distribution between severe traumatic injuries groups was not different at the pre-injury phase (P=0.126) but was significantly different at 6 months post-injury (P<0.001) and at 12 months post-injury (P=0.007) as shown in *Figure 2C*. In the GEE analysis, there was no severe traumatic injury group (P=0.102), time (P=0.246) or group*time interaction (P=0.105) after adjusting for severe head AIS. The adjusted relative risk of poor recovery associated with NIRS are shown in *Table 4*. The model had excellent discrimination but there was poor calibration.

The GOSE distributions between age groups were not different at the pre-injury phase (P=0.364), at 6 months post-injury (P=0.108) and at 12 months post-injury (P=0.171) as shown in *Figure 2D*. The GEE model failed to converge because there was no poor recovery in the paediatric population at both 6 and 12 months.

Additional long-term outcomes were measured by evaluating Glasgow Outcome Scale (GOS) score over time, Disability Rating Scale (DRS) and Care and Needs Scale (CANS) for adult patients and SF-10 for paediatric patients with no associations found. This information is available in the *Supplement content*.

Discussion

This prospective observational cohort study did not show any association between abnormal frontal NIRS-derived cerebral oximetry and long-term outcomes measured by GOSE or short-term outcomes such as 24-hour or 30-day mortality. The other positive findings in this study confirm existing knowledge. The results demonstrate an association between both severe traumatic injuries (ISS > 12) and severe head injury (AIS Head $\geq$ 3) and poor long-term outcome measured by GOSE as well as a higher likelihood of mortality.

A lower mean rSO_2 in the abnormal NIRS group is an expected finding given that the groupings are defined by incorporating values that decrease the mean. There was no association between lower mean rSO_2 and patient outcomes, including those patients with abnormal first CT. This lack of association between abnormal CT and cerebral oximetry values may not be so surprising given varying reports of sensitivity and specificity when comparative cerebral NIRS oximetry is used as a screening tool to detect intracranial haematoma.[15–17]

Even where there is a perceived hint at an association between mean rSO_2 and outcomes, these results are inconclusive. For example, the relative risks (95%CI) of death associated with abnormal NIRS at 24h, 30-days, 6-months and at 12 months postinjury were 4.64 (95% CI: 0.31-69.85). 2.32 (95% CI: 0.47-11.45), 2.29 (95% CI: 0.46-11.27 and 2.14 (95% CI: 0.43-10.56) respectively. Our data do not allow for firm assertions to be made of a real association.

Similarly the finding that rSO_2 derived from the volar forearm did not reveal a difference in peripheral oximetry values between the abnormal and normal cerebral NIRS groups could potentially indicate that NIRS cerebral desaturation was evident even as peripheral perfusion was maintained. However a much larger dataset is required to confirm this finding and any postulated explanation is speculative.

The most significant contributor to the lack of association is the relatively small number of study subjects included although this is consistent with other explorations of the utility of NIRS-derived cerebral oximetry in the context of prehospital anaesthesia and cardiac arrest.[9,18,19]. Recruitment rates were severely limited by the combination of changes to the centralized tasking policies that delayed activation of the clinical team, limited hours of operation of the service and reduced the catchment area to a smaller geographical zone. It was also not feasible to employ a study observer for every shift. It is likely that demonstration of significant associations would require recruitment of a greater number of patients. [16–18]

An additional practical constraint on recruitment was the need to exclude patients where frontal laceration or subcutaneous haematoma precluded sensor placement. This may have excluded some patients who may have displayed cerebral desaturation. This real-world limitation of NIRS cerebral oximetry has not been overcome in any context and any associations or utility will have to be evident even with such patients excluded when applying the monitor in clinical settings.

A further significant contributor to the lack of observed associations appears to be issues with signal collection from the cerebral oximetry sensors. In earlier technical feasibility work we accepted 70% of total prehospital time monitored as a reasonable real-world target.[20] That analysis of the initial 63 included subjects indicated successful capture across 3 sensors in 71.4% of subjects and 90.4% for at least two of three sensors. Other feasibility studies, even in hospital settings, accept monitoring time benchmarks of 80%.[21] Nurmi *et al*, utilising a single sensor

approach, were able to establish successful monitoring in 83% of patients with artefact-free monitoring for an average of 94.5% of the total monitoring time.[9]

This still allows for significant windows where monitoring values are inconsistently captured. Cerebral oximetry values not captured due to artefact could meaningfully affect the ability to demonstrate associations. Our study involved a researcher dedicated to application and maintenance of sensor contact so monitor performance is likely to deteriorate in clinical use. The rigor of our study procedures suggests that recruiting additional subjects is unlikely, as a sole measure, to influence the ability to detect meaningful associations where they exist. The technology itself must improve.

Adding presently available NIRS oximetry devices to prehospital monitoring may create its own risk. The significance of a displayed oximetry value and how a clinician should respond to any abnormality is unknown. If our work identified an association between low rSO_2 and patient outcome this would not provide an immediate guide to treatment. In other clinical settings such as cardiac surgery where low cerebral rSO_2 has been associated with stroke and postoperative cognitive decline, algorithms to address this desaturation have not resulted in altered outcomes.[22,23]

The prehospital environment can be associated with cognitive overload and the addition of a non-additive monitor could substantially increase clinician workload and therefore risk. Inappropriate capture of attention by the new monitor or interference with the ability to integrate the available monitoring information reliably are potential issues.[24,25]

This does not imply that there is no potential for NIRS-derived cerebral oximetry to play a part in future prehospital care. In the hospital, strides are being made to incorporate cerebral oximetry in multimodality monitoring with intracranial pressure monitoring and invasive arterial pressures, and to derive optimal cerebral perfusion and mean arterial pressures specific to the patient.[4,6] Eventually treatment may be informed in real time by direct information about the best conditions for the patient's cerebral tissue and tailored to individual needs. Incorporating multimodality monitoring in prehospital care will require ongoing work in the hospital setting to arrive at an agreed gold standard approach, engineering improvements to NIRS oximetry monitors and greater use of invasive pressure monitoring in this clinical setting.

Conclusion:
This prospective observational cohort study did not demonstrate an association between prehospital NIRS-derived cerebral oximetry and either short-term or long-term functional outcome in patients with TBI or severe traumatic injuries. The ideal cerebral oximeter that is non-invasive and provides clinically meaningful and reproducible measurements across multiple areas of the head without issues created by ambient light, hair, artefact or loss of contact is yet to be developed. Further engineering advances are likely to be necessary to realise any potential in this technology for multimodality monitoring in the prehospital setting. Until that time, NIRS cerebral oximetry is not useful for prehospital clinical use.

Conflicts of Interest:
There are no conflicts of interest to declare for any of the authors.

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Author Contributions:
AW undertook initial study design, data collection and preparation and revision of the manuscript.

EP undertook data collection and revisions of manuscripts.

AG, JS and JE participated in study design and revisions of the manuscript.

AL was involved in initial study design, data analysis and revisions of the manuscript.

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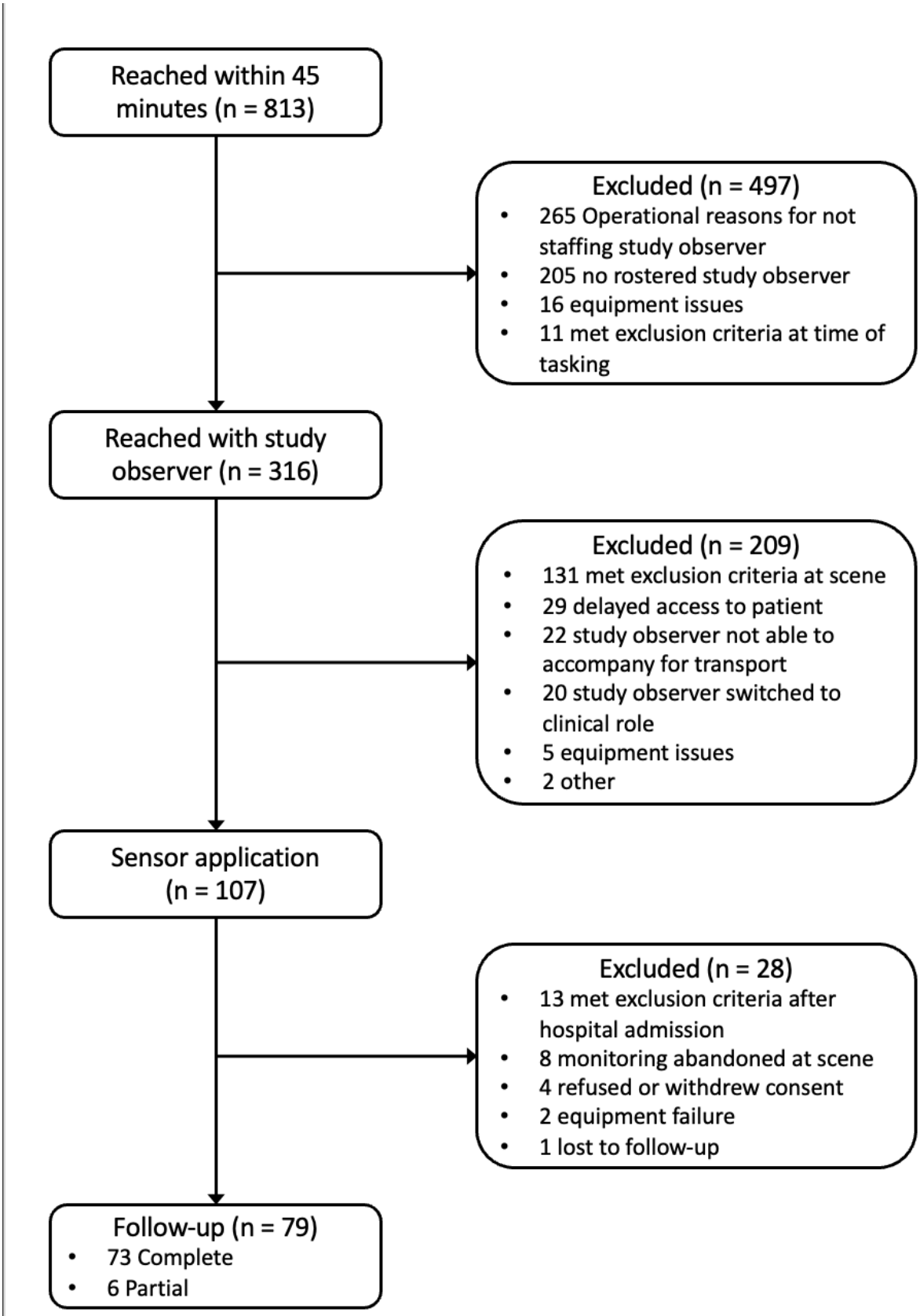


Figure 1: Recruitment Flow Diagram

Table 1. Prehospital phase characteristics of study population by NIRS groups

	All patients (n=79)	Abnormal NIRS (n=14)	Normal NIRS (n=65)	P value
Mean (SD) age, years	37.7 (16.9)	48.2 (17.6)	35.4 (15.9)	0.009
Paediatric (age<16 years), n (%)	11 (13.9)	1 (7.1)	10 (15.4)	0.678
Males, n (%)	57 (72.2)	8 (57.1)	49 (75.4)	0.196
History of anticoagulants use, n (%)	2 (2.6)	0 (0.0)	2 (3.1)	1.000
Preexisting anaemia, n (%)	2 (2.6)	0 (0.0)	2 (3.1)	1.000
History of psychiatric disorder, n (%)	20 (26.0)	6 (46.2)	14 (21.9)	0.088
Prior head injury, n (%)	2 (2.6)	0 (0.0)	2 (3.1)	1.000
Chronic neurological disorder disorder, n (%)	3 (3.9)	2 (15.4)	1 (1.6)	0.072
History of CVA haemiparesis, n (%)	1 (1.3)	1 (7.7)	0 (0.0)	0.169
Mechanism of injury, n (%)				0.841
Motor vehicle accident	13 (16.5)	4 (28.6)	9 (13.8)	
Motorbike accident	25 (31.6)	3 (21.4)	22 (33.8)	
Pedal cyclist	5 (6.3)	1 (7.1)	4 (6.2)	
Pedestrian	5 (6.3)	1 (7.1)	4 (6.2)	
Sports/horse riding	8 (10.1)	1 (7.1)	7 (10.8)	
Falls	13 (16.5)	2 (14.3)	11 (16.9)	
Industrial	2 (2.5)	1 (7.1)	1 (1.5)	
Assault	2 (2.5)	0 (0.0)	2 (3.1)	
Other	6 (7.6)	1 (7.1)	5 (7.7)	
Initial Injury severity score, n (%)				0.077
>15	33 (41.8)	9 (64.3)	24 (36.9)	
⩽15	46 (58.2)	5 (35.7)	41 (63.1)	
Severe traumatic brain injury, n (%)	13 (16.5)	4 (28.6)	9 (13.8)	0.231
Median (IQR) first Glasgow Coma Score	15 (13-15)	14 (12-15)	15 (14-15)	0.363
Prehospital hypotension, n (%)	11 (13.9)	4 (28.6)	7 (10.8)	0.098
Prehospital hypoxia, n (%)	17 (21.5)	6 (42.9)	11 (16.9)	0.066
Prehospital pupillary reactivity, n (%)				0.713
Neither pupil reactive	3 (3.8)	1 (7.1)	2 (3.1)	
Either pupil reactive	1 (1.3)	0 (0.0)	1 (1.5)	
Both pupils reactive	72 (91.1)	13 (92.9)	59 (90.8)	
No assessment in either or both pupils	3 (3.8)	0 (0.0)	3 (4.6)	
Prehospital crystalloid given, n (%)	48 (60.8)	8 (57.1)	40 (61.5)	0.771
Prehospital hypertonic solution given, n (%)	5 (6.3)	1 (7.1)	4 (6.2)	1.000
Prehospital PRBC given, n (%)	4 (5.1)	2 (14.3)	2 (3.1)	0.142
Prehospital anaesthesia given, n (%)	16 (20.3)	1 (7.1)	15 (23.1)	0.279
Prehospital intubation, n (%)	17 (21.5)	2 (14.3)	15 (23.1)	0.722
Median (IQR) time spent at scene, min	20 (14-27)	19 (14-28)	20 (14-28)	0.939
Median (IQR) total prehospital time, min	82 (67-98)	84 (72-95)	82 (67-100)	1.000

Table 2. Hospital phase characteristics of study population by NIRS groups

	All patients (n=79)	Abnormal NIRS (n=14)	Normal NIRS (n=65)	P value
Mean (SD) ED pulse, bpm[a]	91 (20)	87 (21)	91 (20)	0.497
Median (IQR) ED SpO_2 (%)[a]	99 (97-100)	99 (96-100)	100 (97-100)	0.280
Mean (SD) ED SBP, mmHg[a]	132 (22)	123 (23)	133 (21)	0.142
Mean (SD) ED temperature, °C[b]	36.5 (0.7)	36.3 (0.9)	36.5 (0.6)	0.237
Median (IQR) ED GCS[a]	15 (13-15)	15 (14-15)	15 (13-15)	0.857
ED pupillary reactivity, n (%)				0.360
Neither pupil reactive	4 (5.1)	0 (0.0)	4 (6.2)	
Either pupil reactive	3 (3.8)	0 (0.0)	3 (4.6)	
Both pupils reactive	67 (84.8)	12 (85.7)	55 (84.6)	
No assessment in either or both pupils	5 (6.3)	2 (14.3)	3 (4.6)	
ED transfer to destination, n (%)[a]				0.694
Home	3 (3.8)	1 (7.7)	2 (3.1)	
Operating theatres	23 (29.5)	4 (30.8)	19 (29.2)	
Intensive care unit	11 (14.1)	3 (23.1)	8 (12.3)	
High dependency unit	21 (26.9)	3 (23.1)	18 (27.7)	
Ward	20 (25.6)	2 (15.4)	18 (27.7)	
External ventricular drain placed at first operation, n (%)[a]	7 (9.0)	1 (7.7)	6 (9.2)	1.000
Pressure monitor on first operation, n (%)[a]	3 (3.8)	0 (0.0)	3 (4.6)	1.000
Decompressive craniectomy at first operation, n (%)[a]	3 (3.8)	0 (0.0)	3 (4.6)	1.000
Haematoma evacuated at first operation, n (%)[a]	1 (1.3)	0 (0.0)	1 (1.5)	1.000
Some other first operation, n (%)[f]	2 (2.6)	0 (0.0)	2 (3.1)	1.000
Had other surgery in first 24 hours, n (%)	29 (36.7)	6 (42.9)	23 (35.4)	0.761
Admitted to ICU/HDU, n (%)[a]	52 (66.7)	9 (69.2)	43 (66.2)	1.000
Tracheostomy, n (%)	4 (7.7)	0 (0.0)	4 (9.3)	1.000
Median duration of intubation, days	0 (0-3.5)	1.0 (0-4.5)	0 (0-4.0)	0.584
Median duration of ventilation, days	0 (0-3.8)	1.0 (0-5.0)	0 (0-4.0)	0.617
Median (IQR) duration of ICU/HDU stay, days	3.5 (2.0-7.8)	5.0 (3.5-17.5)	3.0 (2.0-7.0)	0.149

Abbreviation: ED = Emergency Department

[a] n=1 missing; [b] n=4 missing; [c] n=9 missing; [d] n=16 missing; [e] n=23 missing; [f] n=2 missing; [g] n=8 missing;

Table 3. Computerized tomography (CT) characteristics in 60 patients by NIRS, 24-hour mortality and 30-day mortality groups

	All patients (n=60)	**Abnormal NIRS (n=10)**	**Normal NIRS (n=50)**	**P value**
First CT Marshall score, n (%)				
Diffuse Injury with no pathology (I)	43 (71.7)	9 (90.0)	34 (68.0)	
Diffuse injury with high or mixed density lesions (II)	12 (20.0)	1 (10.0)	11 (22.0)	
Diffuse injury and swelling (III)	3 (5.0)	0 (0.0)	3 (6.0)	
Diffuse injury and shift (IV)	0 (0.0)	0 (0.0)	0 (0.0)	0.539
Evacuated mass lesion (V)	0 (0.0)	0 (0.0)	0 (0.0)	
Non-evacuated mass lesion (VI)	2 (3.3)	0 (0.0)	2 (4.0)	
Worst CT Marshall score, n (%)				
Diffuse Injury with no pathology (I)	43 (71.7)	9 (90.0)	34 (68.0)	
Diffuse injury with high or mixed density lesions (II)	9 (15.0)	0 (0.0)	9 (18.0)	
Diffuse injury and swelling (III)	4 (6.7)	0 (0.0)	4 (8.0)	
Diffuse injury and shift (IV)	1 (1.7)	1 (10.0)	0 (0.0)	0.119
Evacuated mass lesion (V)	1 (1.7)	0 (0.0)	1 (2.0)	
Non-evacuated mass lesion (VI)	2 (3.3)	0 (0.0)	2 (4.0)	
	All patients (n=60)	**24 h mortality (n=1)***	**24 h survival (n=59)**	**P value**
First CT Marshall score, n (%)				
Diffuse Injury with no pathology (I)	43 (71.7)	0 (0.0)	43 (72.9)	
Diffuse injury with high or mixed density lesions (II)	12 (20.0)	0 (0.0)	12 (20.3)	
Diffuse injury and swelling (III)	3 (5.0)	0 (0.0)	3 (5.1)	
Diffuse injury and shift (IV)	0 (0.0)	0 (0.0)	0 (0.0)	<0.001
Evacuated mass lesion (V)	0 (0.0)	0 (0.0)	0 (0.0)	
Non-evacuated mass lesion (VI)	2 (3.3)	1 (100.0)	1 (1.7)	
Worst CT Marshall score, n (%)				
Diffuse Injury with no pathology (I)	43 (71.7)	0 (0.0)	43 (72.9)	
Diffuse injury with high or mixed density lesions (II)	9 (15.0)	0 (0.0)	9 (15.3)	
Diffuse injury and swelling (III)	4 (6.7)	0 (0.0)	4 (6.8)	
Diffuse injury and shift (IV)	1 (1.7)	0 (0.0)	1 (1.7)	<0.001
Evacuated mass lesion (V)	1 (1.7)	0 (0.0)	1(1.7)	
Non-evacuated mass lesion (VI)	2 (3.3)	1 (100.0)	1 (1.7)	
	All patients (n=60)	**30-day mortality (n=5)***	**30-day survival (n=55)**	**P value**
First CT Marshall score, n (%)				
Diffuse Injury with no pathology (I)	43 (71.7)	0 (0.0)	43 (78.2)	

Diffuse injury with high or mixed density lesions (II)	12 (20.0)	2 (40.0)	10 (18.2)	<0.001
Diffuse injury and swelling (III)	3 (5.0)	1 (20.0)	2 (3.6)	
Diffuse injury and shift (IV)	0 (0.0)	0 (0.0)	0 (0.0)	
Evacuated mass lesion (V)	0 (0.0)	0 (0.0)	0 (0.0)	
Non-evacuated mass lesion (VI)	2 (3.3)	2 (40.0)	0 (0.0)	
Worst CT Marshall score, n (%)				<0.001
Diffuse Injury with no pathology (I)	43 (71.7)	0 (0.0)	43 (78.2)	
Diffuse injury with high or mixed density lesions (II)	9 (15.0)	0 (0.0)	9 (16.4)	
Diffuse injury and swelling (III)	4 (6.7)	1 (20.0)	3 (5.5)	
Diffuse injury and shift (IV)	1 (1.7)	1 (20.0)	0 (0.0)	
Evacuated mass lesion (V)	1 (1.7)	1 (20.0)	0 (0.0)	
Non-evacuated mass lesion (VI)	2 (3.3)	2 (40.0)	0 (0.0)	

* one patient who died did not have CT done

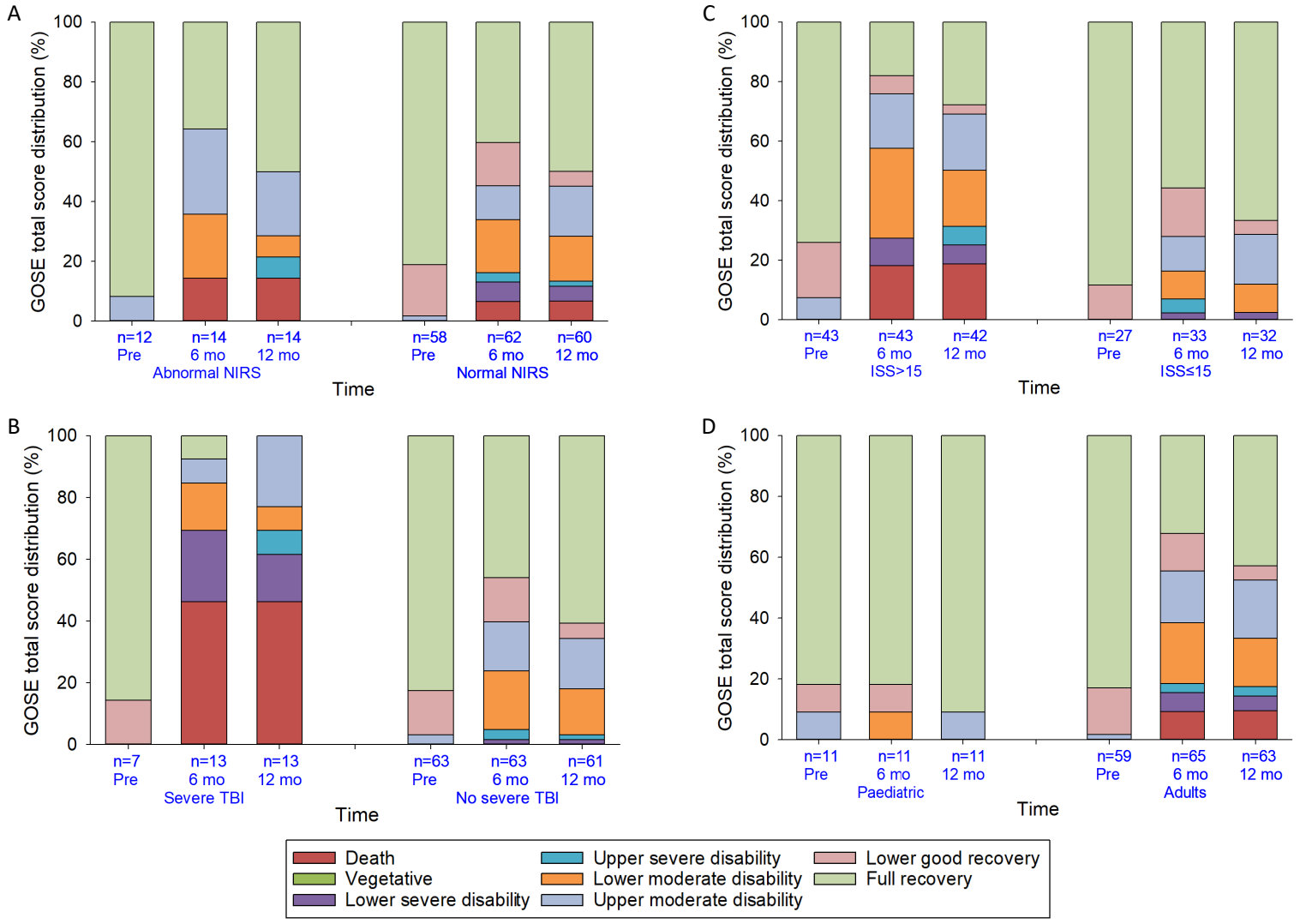
Table 4. Association between various patient groups and Glasgow Outcome Scale Extended (GOSE) over time

Patient Group	Time	Incidence of poor recovery (n, %)	Relative risk (95% CI)*	Discrimination AUROC (95% CI)	Calibration P value
NIRS				0.82 (0.74 to 0.90)	0.403
Normal (n=62)	6 months	10 (16.1)	1.00		
Abnormal (n=14)	6 months	2 (14.3)	0.59 (0.17 to 2.13)		
Normal (n=60)	12 months	8 (13.3)	0.87 (0.69 to 1.11)		
Abnormal (n=14)	12 months	3 (21.4)	0.89 (0.33 to 2.41)		
Severe TBI				0.87 (0.77 to 0.97)	0.877
GCS>12 and head AIS<3 (n=63)	6 months	3 (4.8)	1.00		
GCS≤12 and head AIS≥3 (n=13)	6 months	9 (69.2)	16.28 (3.15 to 84.14)		
GCS>12 and head AIS<3 (n=61)	12 months	2 (3.3)	0.81 (0.25 to 2.61)		
GCS≤12 and head AIS≥3 (n=13)	12 months	9 (69.2)	16.28 (3.15 to 84.14)		
Severity traumatic injury				0.83 (0.73 to 0.93)	0.038
ISS≤15 (n=43)	6 months	3 (7.0)	1.00		
ISS>15 (n=33)	6 months	9 (27.3)	1.63 (0.60 to 4.44)		
ISS≤15 (n=42)	12 months	1 (2.4)	0.48 (0.17 to 1.32)		
ISS>15 (n=32)	12 months	10 (31.2)	1.84 (0.69 to 4.93)		
Age group			Convergence not achieved in model		
Adults (n=65)	6 months	12 (18.5)			
Paediatric (n=11)	6 months	0 (0.0)			
Adults (n=63)	12 months	11 (17.5)			
Paediatric (n=11)	12 months	0 (0.0)			

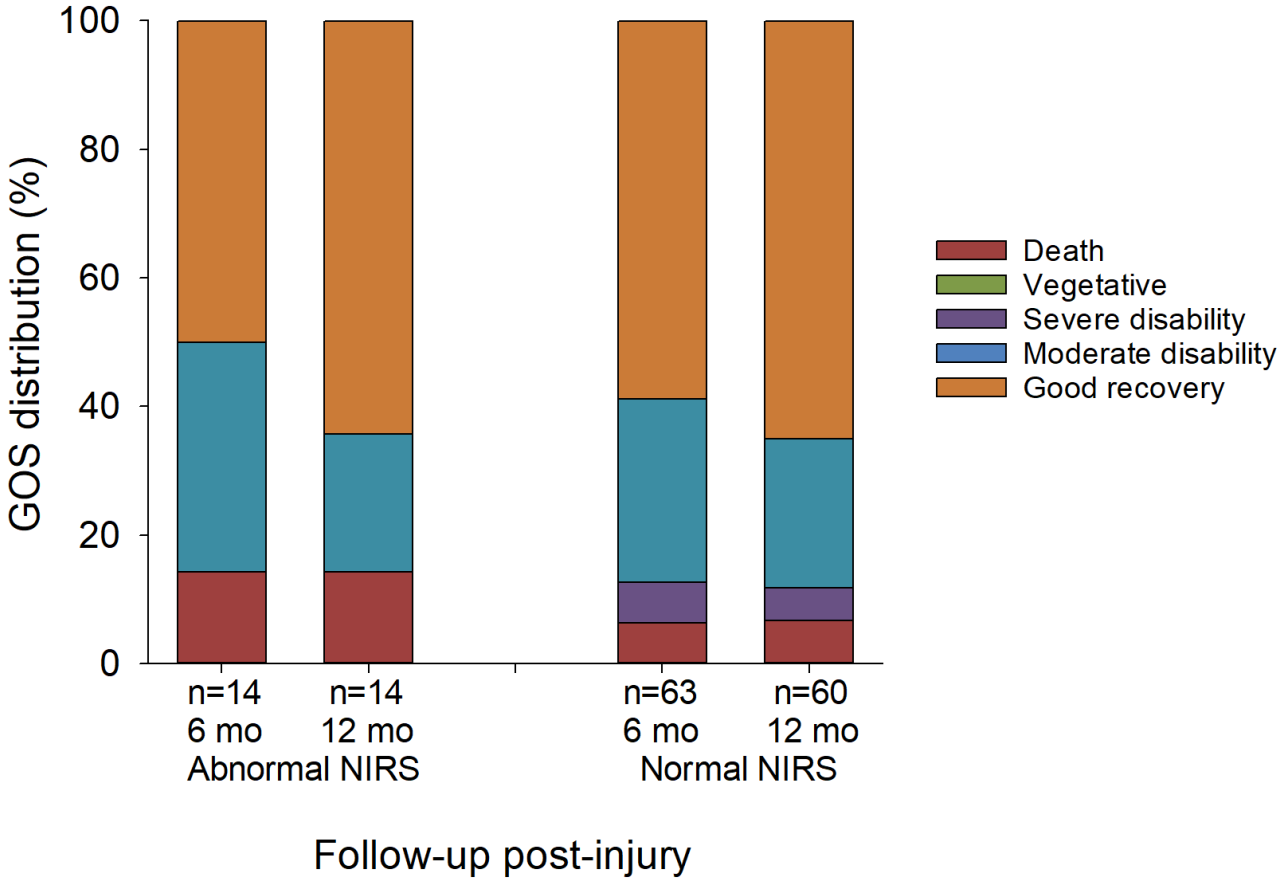
Abbreviations: AUROC, area under the receiving operating characteristic curve; ISS, injury severity score; NIRS, near-infrared spectroscopy; TBI, traumatic brain injury

* Adjusted for severe head AIS

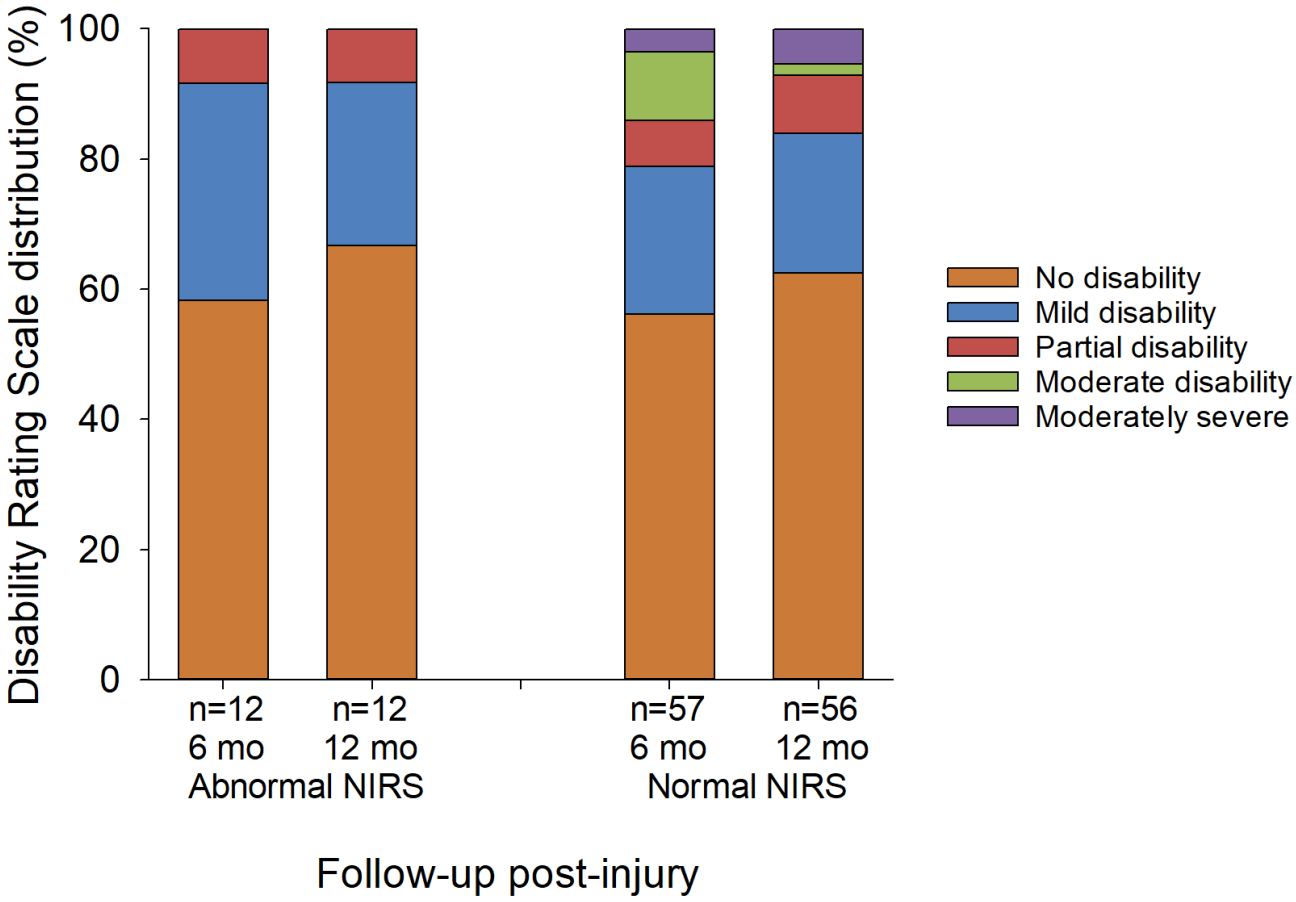
Figure 2. Glasgow Outcome Scale Extended (GOSE) over time (Pre-injury [Pre], 6 months post-injury [6 mo], 12 months post-injury [12 mo]) by various patient groups (A) NIRS (B) severe TBI (C) ISS (D) Age



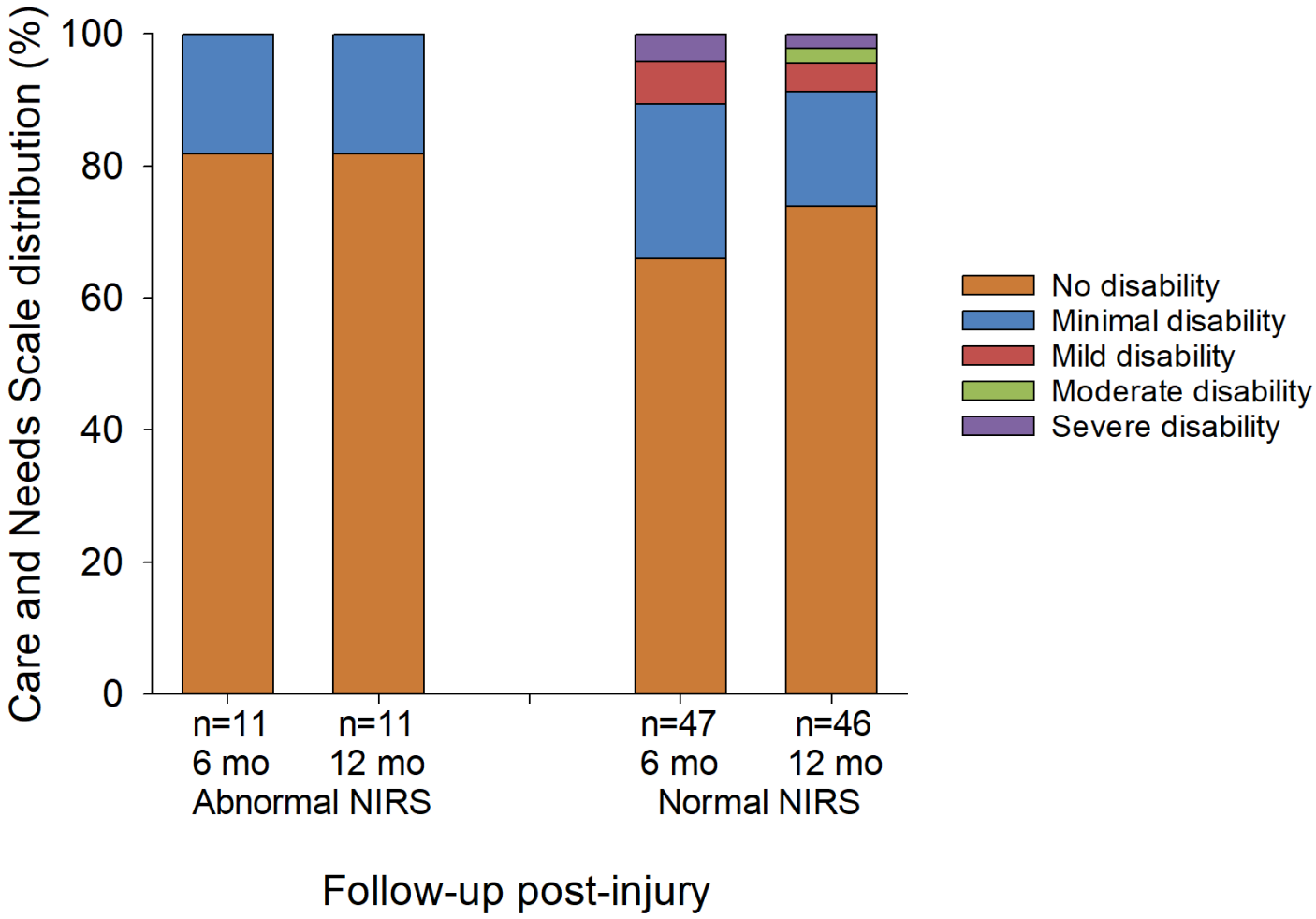
Supplementary content Figure 1. Glasgow Outcome Scale over time (6 months post-injury [6 mo], 12 months post-injury [12 mo]) by NIRS groups



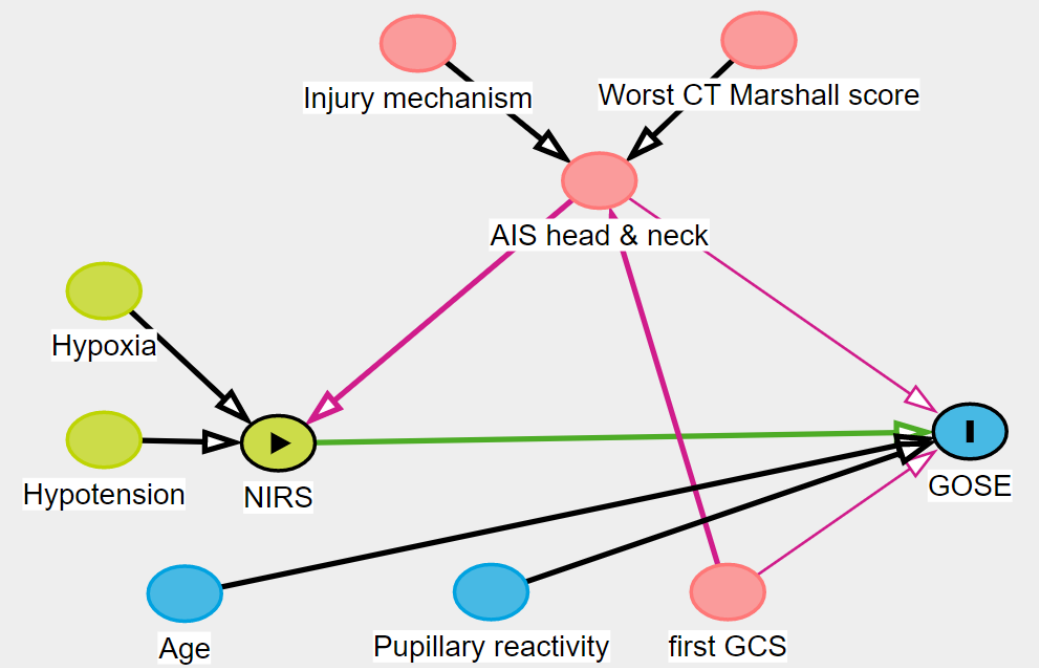
Supplementary content Figure 2. Disability rating scale over time (6 months post-injury [6 mo], 12 months post-injury [12 mo]) by NIRS groups



Supplementary content Figure 3. Care and Needs Scale over time (6 months post-injury [6 mo], 12 months post-injury [12 mo]) by NIRS groups



Supplementary content Figure 4 Directed acyclic graph for association between near infrared spectroscopy and Glasgow Outcome Scale Extended



Minimal sufficient adjustment sets for estimating the total effect of NIRS on eGOS:

- AIS head & neck

Chapter 6

Novel Data Processing Approaches for Cerebral Oximetry in Prehospital Traumatic Brain Injury

This chapter of the thesis has been submitted to *Acta Anaesthesiologica Scandinavica* for publication as:

Weatherall AD, Argha A, Poynter E, Garner A, Skowno J, Egan J, Lovell NH. Three Approaches to Analysis of Prehospital Noninvasive Cerebral Oximetry Measurements: Statistics, Machine Learning and Deep Learning Methods.

The submitted manuscript is reproduced here.

Title: Three Approaches to Analysis of Prehospital Noninvasive Cerebral Oximetry Measurements: Statistics, Machine Learning and Deep Learning Methods

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Short title: Novel analysis of prehospital cerebral oximetry

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Abstract:

Background:

Traumatic brain injury is a significant management challenge in prehospital medicine with no current ability to provide monitoring information directly interrogating cerebral tissue. Near-infrared spectroscopy (NIRS) tissue oximetry monitoring can provide noninvasive monitoring of cerebral tissue, however its optimal use in the clinical setting is unclear.

Aim:

The aim of this study was to explore the value of novel approaches to analysis of NIRS tissue oximetry measurements in a prehospital trauma population.

Methods:

A prospective observational cohort study was conducted in patients with traumatic injuries in the setting of an advanced prehospital emergency medical service utilising the Nonin EQUANOX 7610 monitor. Patient outcomes included Glasgow Coma Scale (GCS), Abbreviated Injury Score (AIS) (Head and Neck) $\geq$ 3 and mortality at 30 days. Recorded data were analysed using a standard statistical model, a machine learning (ML) approach utilising manually selected features for extraction, and a convolutional neural network analysis as an example of a deep learning (DL) approach.

Results:

Both standard statistical analysis and a simple ML analysis were not able to establish any meaningful associations or demonstrate predictive ability in any of the outcome groups. The DL approach demonstrated some predictive ability for GCS and AIS outcomes with performance further improved by fusion of results across additional data streams.

Conclusions:

A deep learning approach to analysis of NIRS tissue oximetry measurements demonstrated improved predictive ability compared to simple ML. This may represent a pathway to utilising NIRS cerebral oximetry to provide real time information that clinicians can act upon in looking after patients. Larger datasets and improved data monitoring capture are required for further exploration of this approach.

Introduction:
Traumatic brain injury (TBI) is a major contributor to morbidity and mortality globally. Associated healthcare costs are distributed unequally with a greater proportional burden on developing countries but have been estimated as being as high as $US400 billion annually [1–3].

Prehospital treatment for patients with TBI centres on ensuring key physiological parameters are within the bounds suitable for the general population. Guidelines support avoidance of hypoxia and hypotension as these are associated with worse patient outcomes [4]. Both are key factors in worsening the secondary brain injury that evolves over time.

However, blood pressure targets in particular are based on observational studies showing worse outcomes when patients fall outside these population-level ranges [5,6]. Targets to optimise global conditions for oxygen delivery, oxygenation with adequate pressure, do not automatically translate to optimal conditions at the level of cerebral tissue. The ideal situation for the clinician would be to have a simple to use, non-invasive monitor that could highlight meaningful physiological trends specific to cerebral tissue in real time, and then prompt intervention, such as changes to oxygenation, ventilation and blood pressure.

Near-infrared spectroscopy (NIRS) is of interest for this reason. NIRS applies principles relating to differential absorption of light in the 750-810 nm wavelength range by different chromophores in tissues. This allows the technology to provide a measurement of regional oxygen saturation, which is influenced by global oxygenation, oxygen delivery to tissues and the contribution of arterial and venous circulation to the overall oxygenation state of the tissue. It also permits measurement of total haemoglobin (HbI), within an area of tissue, which is a correlate for blood volume within that area.

NIRS oximetry meets some of the requirements of the ideal prehospital monitor. Commercially available monitors are portable, applied through non-invasive means and provide high level information relating to oxygenation and perfusion. There has been some investigation of prehospital applications of NIRS in intracranial haematoma detection and circulatory monitoring after out-of-hospital cardiac arrest [7–13]. There is no published information on prehospital use of NIRS cerebral oximetry to evaluate cerebral physiology in TBI patients.

NIRS cerebral oximetry has been evaluated in other clinical settings. In cardiac surgery low indices of cerebral oxygenation are associated with stroke and postoperative cognitive decline though algorithms to maintain regional tissue oxygen saturation (rSO_2) have shown mixed results in improving outcomes [14–16]. An area with promise in TBI is incorporation of noninvasive cerebral oximetry into multimodality monitoring to determine optimal cerebral perfusion pressure and mean arterial pressure for patients [17,18]. However multimodal monitoring requires invasive pressure measurements for both arterial pressure and intracranial pressure and is presently impractical for prehospital care.

The aim of this study was to explore the utility of statistical, machine learning (ML) and convolutional neural network (CNN) approaches in the analysis of NIRS-derived cerebral oximetry data in the context of TBI.

Methods:
This exploratory analysis was undertaken as part of a prospective cohort study approved by the Sydney Children's Hospital Network Human Research Ethics Committee (reference 11/SCHN/212). An initial waiver for consent to data collection was provided. Consent was subsequently affirmed during follow-up from either the subject themselves or, where more appropriate, a family member.

Subject recruitment was undertaken via CareFlight, Sydney, Australia. The service delivers rapid response trauma care in response to mission tasking from a separate dispatch system. Patients may be transported to hospital by rotary wing or road ambulance transport. The clinical team comprises an advanced care paramedic and critical care physician with the ability to provide advanced assessment including point-of-care ultrasound, advanced life support, anaesthesia, intubation and ventilation, blood product transfusion and other critical care interventions at the scene of the incident or during patient transport.

All patients where patient contact was within 45 minutes of the injury and who were being transported to the trauma centre by the clinical team were considered for inclusion during the period of the study when a study observer was available. Exclusion criteria were:

- Patients < 1 year old or > 70 years old;
- Patients with pre-existing neurological disease or neurological trauma;
- Patients with no trauma mechanism (e.g. drowning, medical complaints);
- Patients with forehead haematomas or lacerations precluding NIRS sensor application;
- Patients where follow-up consent was not obtained.

Exclusion criteria could be applied at the scene or at the point of later data collection.

After the initial study protocol development recruitment dispatch parameters for CareFlight were altered by the central tasking authority [19]. This resulted in a substantial decrease in recruitment rates in comparison to the original projections. After consideration of the parameters considered in calculation of the sample size as per the original protocol, study recruitment was paused after proceeding from 6th July 2014 to 4th November 2018 and available data was analysed as a pilot study.

The NIRS oximetry monitor utilised was a Nonin EQUANOX 7610 Regional Oximetry Monitor (TM Nonin Medical, Inc.). A trained researcher distinct from the clinical team applied monitor sensors as soon as possible after patient contact. This researcher confirmed data capture and monitored adequacy of sensor contact. The clinical team were blinded from NIRS values with the monitoring screen displaying only presence or absence of oximetry signal.

Regional oximetry sensors were applied to the left (Channel 1) and right (Channel 2) frontal regions of the head. An additional sensor was placed on the left volar forearm to assess peripheral vascular bed oxygenation (Channel 3). Each sensor recorded a value every 4 seconds for rSO_2, HbI, oxyhaemoglobin ($CHbO_2$) and deoxyhaemoglobin (CHb).

Patient demographic data, incident data and initial clinical observations such as initial Glasgow Coma Scale (GCS) score were obtained as part of the routine information available at the time of injury and via hospital follow-up. Hospital-based outcome data was collected by direct review of patient records and trauma databases at receiving hospitals. This included Injury Severity Score (ISS) and Abbreviated Injury Scores (AIS) for each body region, 30-day mortality and findings on initial cerebral imaging with computerised tomography (CT) or magnetic resonance imaging (MRI).

Analysis methodologies were tested against the following patient outcomes:

- Mortality at 30 days.
- Initial GCS < 12.
- AIS (head and neck) $\geq$ 3

Statistical Analysis

All data underwent normality testing through the single-sample Kolmogorov-Smirnov goodness-of-fit hypothesis test and Lilliefors' composite goodness-of-fit test. In cases of normality, we used a one-sample t-test with a null hypothesis stating that the mean is zero. In cases where data did not follow a normal distribution, the Wilcoxon rank-sum test for equal medians was employed.

Simple Machine Learning Analysis

All NIRS oximetry records were individually reviewed to remove likely artefact, along with exclusion of the initial 20 seconds of readings to specifically exclude edge artefact while establishing stable measurements.

To soften the NIRS cerebral oximetry data we used a Savitzky–Golay filtering method using the 'smooth' command in Matlab with 'rloess' (which is less sensitive to outliers compared to 'loess') with a span of 5% of the total number of data points.

Manual feature extraction was undertaken utilising clinical set-points defined in the initial protocol.

The following six features were extracted from rSO_2 signals:
(1) Area under the curve of all ≤ 45% segments lasting more than 1 min;
(2) Number of ≤ 45% segments lasting more than 1 min;
(3) Sum of periods ≤ 45% in seconds;
(4) Maximum length of ≤ 45% segments lasting more than 1 min;
(5) Minimum rSO_2; and,
(6) Mean rSO_2.

The following six features were extracted from HbI measurements:
(1) Area under the curve of all ≤ 1 g/dL segments lasting more than 1 min;
(2) Number of ≤ 1 g/dL segments lasting more than 1 min;
(3) Sum of periods ≤ 1 g/dL in seconds,
(4) Maximum length of ≤ 1 g/dL segments lasting more than 1 min;
(5) Minimum of HbI; and,
(6) Mean of HbI.

We employed two ML techniques to predict the outcomes defined before using a holdout validation technique, i.e., the dataset was split into two subsets: the training set (70% of recordings) and the validation set (30% of recordings) which was used to confirm that the model was appropriate when applied to unseen data and therefore generalisable. Specifically, we utilised logistic regression and support vector machines (SVMs) to analyse the data and make predictions based on their respective strengths in handling classification tasks.

Convolutional Neural Network Analysis

For this analysis we leveraged one-dimensional (1D) CNNs to extract intricate patterns from the input NIRS oximetry signals, enabling the capture of nuanced relationships and improved

prediction accuracy [20]. In contrast to ML methods trained on manual feature extraction from the filtered signals, this deep learning (DL) model is an end-to-end learning-based method, meaning that it automatically extracts features from the raw signals without a prior classification being provided. The training set was again 70% of recordings with a validation set comprising 30% of recordings.

As CNNs require fixed-length inputs, pre-processed signals cannot be fed directly into the network as each recording is of different length. We used a zero-padding technique to overcome this issue. The custom 1D CNN developed for this analysis included an input layer, followed by two convolutional layers, a dropout layer, a global-average-pooling layer, and a dense layer. A batch normalisation layer was placed after each convolutional layer to improve the generalisability. The kernel size, the number of kernels and the stride in the first and second convolutional layers were (5,50,1) and (10,100,1), respectively. The rectified linear unit (ReLU) activation function was used for the convolutional layers and fully connected layer. We trained the DL models for 500 epochs. The optimiser used to train the CNNs was 'adam' with an initial learning rate of 0.01 [21].

The CNN technique was applied to each of rSO_2, HbI, $ChbO_2$ and CHb as well as being applied as a fusion model using all four data streams simultaneously.

Results:
Of the 813 patients with injuries between 6th July 2014 to 4th November 2018, 79 were in the initial analysis after applying the exclusion criteria (*Figure 1*). After preprocessing a further 4 records had a total period of NIRS cerebral oximetry data collection of <1 minute and were excluded from the final analysis against specific outcomes. 75 subjects were included in the analysis related to both GCS and 30-day mortality. 34 subjects had a value recorded for AIS, indicating some form of head injury. These scores were grouped into minor head injury (AIS (Head and Neck) < 3) and serious head injury (AIS (Head and Neck) $\geq$ 3).

Results of Statistical Analysis
Application of statistical analysis approaches to both rSO_2 and HbI values did not reveal any significant associations between the extracted values and mortality at 30 days, GCS < 12 or AIS (Head and Neck) $\geq$ 3 (see *Table 1*).

Machine Learning Analysis
Neither logistic regression or SVMs demonstrated any predictive ability linking NIRS oximetry data to mortality at 30 days, GCS < 12 or AIS (Head and Neck) $\geq$ 3. This is reflected in *Table 2*.

Convolutional Neural Network Analysis
CNNs demonstrated precision and accuracy that was improved compared to simple ML (*Table 2*). This was evident for rSO_2 and HbI for both optode positions for both GCS outcomes and AIS (Head and Neck) $\geq$ 3. In channel 1, but not channel 2, CNN displayed predictive characteristics for mortality at 30 days whereas both statistical analysis and simple ML could not demonstrate associations. Precision and accuracy increased further utilising the CNN fusion approach combining rSO_2, HbI, $ChbO_2$ and CHb.

Discussion:
In this exploratory analysis there was no evident association between rSO_2 or HbI values and GCS < 12, AIS (Head and Neck) $\geq$ 3 or 30 day moraltity when the available data were analysed utilising either a standard statistical approach or a simple ML approach. However, application of DL using a CNN led to enhanced precision and accuracy of the predictive model utilising rSO_2 and HbI when evaluated against the GCS < 12 and AIS outomes. The CNN model also generated precision and accuracy values for Channel 1 when tested against mortality at 30 days, despite limited samples in this dataset.

The finding that application of DL to this small dataset is capable of establishing predictive ability may offer a novel pathway to establishing a useful clinical role for NIRS cerebral oximetry. Progress in defining the best clinical use of NIRS has been slow. This lack of progress may be resolved by analysis that allows nuanced pattern recognition that have not previously been applied to these datasets.

The DL approach interrogates the available monitoring signals and then defines significant features itself through repeated learning after the provision of the initial inputs. It then utilises these features that would be otherwise hidden to the clinician's eye as the basis to classify each set of data into the chosen outcome categories. This provides a plausible explanation for the superior performance of DL compared to simple ML. In the simple ML approach, extracted features were designated by the research team. However some of those features contained limited values and therefore were non-contributory. CNN is an example of an end-to-end system that can define useful features for extraction and disregard non-contributory features. In this analysis it was able to establish precision and accuracy where simple ML could not. It learnt more efficiently and with greater accuracy than a system given defined parameters by the research team.

Each of the chosen patient outcomes have direct relevance to clinical care. A prognostic association between non-invasive cerebral oximetry and 30-day mortality could act as a prompt to prioritise neuroprotection in significantly injured patients and aid informed decision-making at the hospital. Any association with GCS on the basis of an observed difference in either rSO_2 or HbI could potentially help differentiate between milder forms of TBI and more serious insults or flag a patient at risk of deterioration from normal GCS to a score below 12.

An association with severe head injury could be particularly important as it might prompt more rapid cerebral imaging on arrival at hospital to assess the role of neurosurgery or intracranial pressure monitoring. This outcome group represents the most likely cohort to demonstrate changed signals in the NIRS oximetry record as this specific group contains those with significant injury that is likely to be evolving throughout the prehospital phase. Yet in this clinical situation where signal change might be expected, only DL showed any predictive ability.

There are a number of potential contributors to the lack of demonstrated association with both the statistical analysis and ML approach. As part of a pilot study there are limited numbers of records on which to base the analysis. In the context of the aims of the study this is a reasonable approach and earlier publications with initial descriptions of the utilisation of NIRS in developing cerebrovascular reactivity indices were based on fewer patients [22,23]. The limited numbers in this pilot are also offset by evaluation against outcomes likely to be associated with significant injury, particularly AIS (Head and Neck) $\geq$ 3 which would make it more likely that signals would be altered.

An additional practical constraint on recruitment was the need to exclude patients where frontal laceration or subcutaneous haematoma precluded sensor placement may have excluded some patients who may have displayed cerebral desaturation. This real-world limitation of NIRS cerebral oximetry has not been overcome and any associations or utility will have to be evident even with such patients excluded when applying the monitor in clinical settings.

A further significant contributor to the lack of association likely relates to interruptions of monitoring signal. Analysis of successful signal capture undertaken in an initial dataset accepted technical feasibility of successful monitoring for more than 70% of the total prehospital time with this threshold reached across both cerebral channels 74.6% of the time [24]. This is pragmatic in a prehospital context but also means that there are significant gaps in the captured data. The total duration of each recording is also relatively brief compared to the epochs that can be achieved in a hospital setting [17,25]. This combination of factors contributing to limited data sets is particularly significant for both the statistical analysis and the ML approaches, with some of the extracted features dependent on extremely limited numbers.

However our finding that the CNN approach was able to discern predictive associations with limited datasets hints at a path worth further exploration. There is some precedent suggesting that the approach to analysing or combining data obtained from physiological measurement is critical to making the best use of NIRS cerebral oximetry. The traditional focus on rSO_2 alone has not translated into information that can prompt direct measures from clinicians to improve patient outcomes. Approaches that incorporate other measurements to develop correlation indices that provide insights into cerebrovascular reactivity or optimal cerebral perfusion pressure or mean arterial pressure all offer much promise for in-hospital care [22,23,25].

These approaches generally involve measurements taken over 30 to 60 minutes or reliant on multiple invasive pressure measurements and are therefore impractical for prehospital care. Application of a deep learning approach that provides pattern recognition at a level beyond the discernment of the clinician would be a breakthrough. Recognition of otherwise hidden patterns that are also clinically meaningful may allow for the development of real-time flagging of significant physiological signals that practitioners could otherwise not identify. Real-time changes would then allow immediate changes to clinical care.

However, it is critical that clinicians develop an understanding of the potential limitations of the DL approach itself. The ML approach described involves manual extraction of defined features guided by available literature with a clear link to relevant clinical parameters. The CNN approach involves initial training with clinical datasets but it is the system that then defines the associations. The precise manner in which it has arrived at the predictive association is initially hidden as the involvement of a range of intricate layers and parameters creates a “black box” effect.

It is possible to apply explainable artificial intelligence methods (XAI) to address this challenge. Methods such as layer-wise relevance propagation, saliency maps, and gradient-based attribution techniques aid interpretability by highlighting relevant regions in input signal or identifying influential neurons within the network [26]. This step will therefore become an essential step in further development of the CNN approach. These XAI techniques are applied to CNNs to make their operation more transparent and understandable, enhance trust in the CNN-based models and also facilitate the engagement of domain experts to validate the decisions made by the model, identify any biases and improve model performance and generalisability.

In the context of applying CNNs to cerebral oximetry, or other monitoring systems, XAI techniques will therefore become a critical step in ensuring that the decisions made by the model are directly linked to meaningful clinical parameters or patient outcomes. It is notable that in our application of the ML approach the features identified in advance were not contributory to patient classification into the outcome groups. A DL technique with application of XAI techniques may assist clinicians and researchers in arriving at a better understanding of which signals have been assessed by the model as important and in doing so identify the key parameters that warrant further investigation. The DL approach itself prompts learning for those interrogating the system's processes.

To further explore the deep learning approach a number of key requirements must now be met. The overall reproducibility and validity of CNN approaches are reliant on much larger datasets, in part to ensure that it is not the small size of the dataset itself that has created this observed result. This will require much higher rates of signal acquisition from the NIRS monitor itself. Presently available monitors cannot achieve adequate reliability of measurement in the prehospital environment for this to be the appropriate setting for this work. The monitors themselves need to improve.

Larger datasets will also require much larger numbers of subjects. This is not feasible in the prehospital environment. Although the prehospital environment represents a unique pathophysiological epoch worthy of focused and specific research, the next step in exploring how to analyse NIRS cerebral oximetry data must return to the hospital setting. The disadvantage of this approach is that a significant time period where TBI is evolving will likely have already occurred before data acquisition. Initial prehospital care, emergency department resuscitation and possibly cerebral imaging, critical care interventions and surgery will likely have already occurred before data acquisition commences. This may well be too late to capture changes as they happen and instead reflect physiology after the established injury. However, until there is a deeper understanding of how to analyse NIRS cerebral oximetry data in a way that empowers clinicians to meaningfully alter their treatment there appears to be limited value in further small studies in the prehospital setting.

Conclusions:
A range of analysis approaches to NIRS cerebral oximetry in the setting of prehospital TBI was described. A novel application of a DL approach established acceptable predictive value. This suggests a path for further exploration with the potential to establish a useful role for NIRS cerebral oximetry however this exploration requires much larger datasets derived from hospital-based research.

Authorship Statements:
AW undertook initial study design, data collection and preparation along with drafting and revision of the manuscript.

AA participated in study design, data preparation and processing, results analysis and reviewed the manuscript.

EP undertook data collection and revisions of manuscripts.

AG, JS, JE and *NL* were involved in initial study design and revisions of the manuscript.

Conflicts of Interest:
There are no conflicts of interest to declare for any of the authors.

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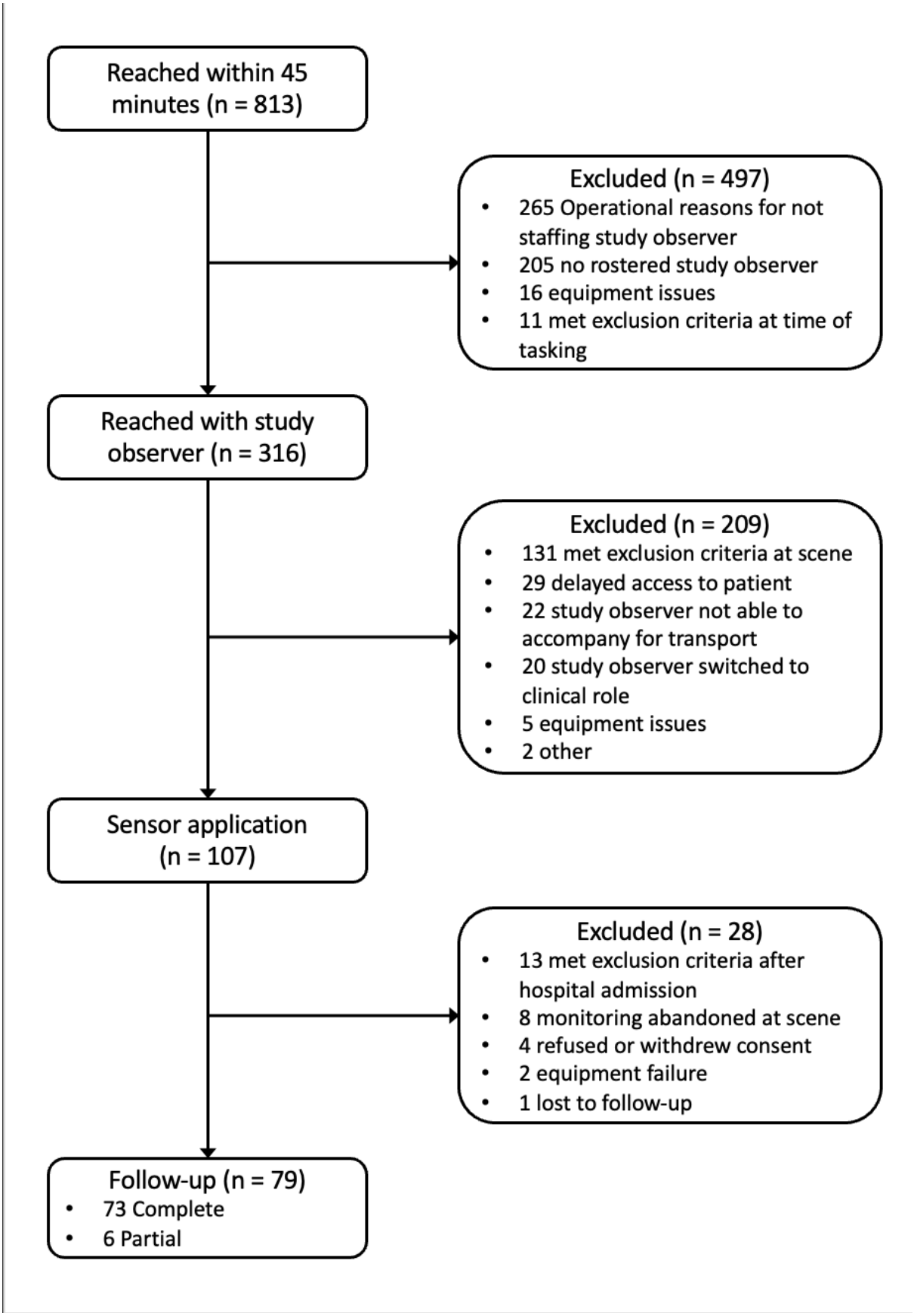

Figure 1: Recruitment flow diagram

		GCS ≤ 12 or > 12		***AIS (Head and Neck) ≥ 3 or < 3***		***30-day mortality***	
		t-test[2]	*Ranksum*	*t-test*[2]	*Ranksum*	*t-test*[2]	*Ranksum*
Channel 1	Minimum rSO_2 (%)	p = 0.86	p = 0.57	p = 0.41	p = 0.61	p = 0.53	p = 0.56
	Mean rSO_2 (%)	p = 0.36	p = 0.48	p = 0.55	p = 0.47	p = 0.65	p = 0.52
	Minimum HbI (g/dL)	p = 0.51	p = 0.23	p = 0.46	p = 0.48	p = 0.99	p = 0.63
	Mean HbI (g/dL)	p = 0.36	p = 0.13	p = 0.27	p = 0.17	p = 0.87	p = 0.34
Channel 2	Minimum rSO_2 (%)	p = 0.43	p = 0.19	p = 0.42	p = 0.9	p = 0.65	p = 0.56
	Mean rSO_2 (%)	p = 0.43	p = 0.19	p = 0.42	p = 0.9	p = 0.65	p = 0.52
	Minimum HbI (g/dL)	p = 0.94	P = 0.74	p = 0.10	p = 0.03	p = 0.17	p = 0.23
	Mean HbI (g/dL)	p = 0.24	p = 0.15	p = 0.4	p = 0.71	p = 0.57	p = 0.68

Table 1 : Results of statistical analysis utilising regional tissue oxygen saturation (rSO_2) and total haemoglobin index (HbI).

		GCS < 12			***AIS (Head and Neck) ≥ 3***			***Mortality at 30 days***		
		Accuracy	*Precision*	*F1 score-macro*	*Accuracy*	*Precision*	*F1 score-macro*	*Accuracy*	*Precision*	*F1 score-macro*
Channel 1 rSO2 (%)	SVM	0.87	NaN	NaN	0.5	0.31	NaN	0.95	NaN	NaN
	Logistic Regression	0.87	NaN	NaN	0.5	0.31	NaN	0.95	NaN	NaN
	CNN	0.78	0.6	0.6	0.58	0.56	0.56	0.57	0.57	0.47
Channel 1 HbI (g/dL)	SVM	0.82	NaN	NaN	0.5	0.31	NaN	0.95	NaN	NaN
	Logistic Regression	0.82	NaN	NaN	0.5	0.31	NaN	0.95	NaN	NaN
	CNN	0.56	0.56	0.5	0.67	0.67	0.66	0.73	0.54	0.52
Channel 1 $CHbO_2$ (g/dL)	CNN	0.56	0.48	0.45	0.58	0.72	0.58	0.77	0.55	0.54
Channel 1 CHb (g/dL)	CNN	0.56	0.56	0.5	0.58	0.61	0.58	0.63	0.52	0.46
Channel 1 Fusion	CNN	0.72	0.63	0.63	0.67	0.67	0.66	0.77	0.55	0.54
Channel 2 rSO2 (%)	SVM	0.87	NaN	NaN	0.67	0.63	0.63	0.95	NaN	NaN
	Logistic Regression	0.87	NaN	NaN	0.6	0.6	0.6	0.95	NaN	NaN
	CNN	0.72	0.63	0.63	0.56	0.58	0.55	0.91	0.48	NaN
Channel 2 HbI (g/dL)	SVM	0.87	NaN	NaN	0.6	0.6	0.58	0.95	NaN	NaN
	Logistic Regression	0.8	0.43	NaN	0.5	0.54	0.5	0.95	NaN	NaN
	CNN	0.78	0.66	0.78	0.89	0.88	0.88	0.82	0.47	NaN
Channel 2 ChbO2	CNN	0.5	0.46	0.41	0.58	0.56	0.56	0.72	0.47	NaN
Channel 2 CHb	CNN	0.83	0.71	0.73	0.44	0.5	0.44	0.91	0.48	NaN
Channel 2 Fusion	CNN	0.83	0.69	0.65	0.78	0.67	0.68	0.91	0.48	NaN

Table 2: Results of simple ML and CNN analysis of NIRS oximetry data. $CHbO_2$ is a measure of oxygenated haemoglobin in the sampled area. CHb is a measure of deoxygenated haemoglobin in the sampled area. ML results are shaded yellow. CNN results are shaded green. 'NaN' is generated when there are insufficient points of data in the extracted features to generate predictive ability. For all outcomes with the exception of mortality at 30 days, CNN analysis is generates predictive ability where ML cannot. Predictive ability improves with fusion of rSO_2, HbI, $CHbO_2$ and CHb.

Chapter 7

Discussion

At the time of a traumatic brain injury, those clinicians caring for patients in the prehospital setting are left with no direct information about any evolving pathology at the level of the brain which might help them deliver the right care at the right moment. The appearance of NIRS as a monitor of organ perfusion and oxygenation would appear to hold great promise as a solution to this problem. If capable of capturing adequate information it offers the potential for use as a non-invasive, rapidly applied monitor that can supplement clinical assessment and other available monitoring by providing direct information about the physiological status of the brain. This thesis has explored the potential for NIRS-derived cerebral oximetry to be utilised in the prehospital environment to provide meaningful indications of patient outcome or information flagging evolving pathology.

Imposed Changes on the Ideal Study Protocol

The work presented in this thesis represents a comprehensive account of multiple elements of the exploration of the clinical utility of NIRS tissue oximetry in the prehospital environment. However it is relevant to note that external limitations placed on the clinical service within which this research was conducted, CareFlight, had a significant impact on the project. Changes to utilisation of the service, tasking policies and practices, geographical constraints and reduction in the total pool of potential patients all contributed to a substantial reduction in clinical activity compared to that anticipated. The effect of this was to introduce a substantial difference in the total number of study

subjects recruited to include in data analysis compared to the ideal study protocol as planned and presented in Chapter 3.

This reduction is highly relevant to the subsequent explorations of any associations between cerebral oximetry and patient outcomes, or of the potential role of novel analysis methods in evaluating measured NIRS tissue oximetry parameters. While it is not the sole limitation relevant to interpreting the data presented within the thesis, it is a significant constraint as described in each relevant section and in the discussion that follows.

Clinical Context at the Time of Study Design

The original study protocol was developed in the context of the operational procedures of the Head Injury Retrieval Trial.[199,200] Activation of the clinical team was triggered on a protocolised basis by the HEMS team who were actively reviewing emergency system calls as they were logged to the centralised computer system. The result was an ability to initiate randomisation to either standard or HIRT-intervention within five minutes of the start of the first phone call to emergency services. Coupled with the launch characteristics of the service, this allowed a median response time anywhere in the Sydney basin of 12 minutes. As the activation protocol prioritised patients with mechanisms likely to result in head injury, the anticipated ongoing yearly patient treatment numbers exceeded 500 total patients per year.

In this context, proceeding with a prospective observational study where a study observer accompanied the treating team to initiate monitoring with NIRS tissue oximetry was a logical progression. The original study protocol included:

- Estimates that recruiting around 1200 study subjects could be achieved in a reasonable time period, given an anticipated case rate of at least 500 per year;
- A requirement for interim evaluation to confirm successful signal capture with the chosen NIRS oximetry monitor, as presented in Chapter 4;
- Data analysis consistent with the statistical analysis approaches presented in the literature at the time, as presented in Chapter 5;
- Exploration of novel analysis techniques that might more closely reflect evolving pathology, as presented in Chapter 6.

Impact of Tasking System Changes

Shortly after commencing this work utilising the PHANTOM study protocol presented in Chapter 3, NSW Ambulance made a decision to alter the operating parameters of CareFlight. These changes included:

- Blocking of access of the CareFlight clinical team to review potential cases as calls were received to the coordination centre.
- Cessation of the use of protocolised tasking.
- Acceptance of an elongated time to activate the CareFlight team, permitting activation at any time rather than confining the tasking initiation time constraint to less than eight minutes as had previously been the case.
- A prohibition from CareFlight attending all incidents south of a geographical border defined by a local motorway two kilometres south of the CareFlight facility. This decreased the catchment area for the clinical service by 100 kilometres to the south.
- An effective exclusion of half of the population of Sydney from the catchment area of the study.

These changes resulted in a number of detrimental effects in the context of this research:

- Total case numbers immediately decreased to below 300 per year.
- The proportion of patients attended by CareFlight clinicians who had experienced TBI was dramatically reduced.
- Delays in tasking created by waiting for central review substantially altered the 'time from emergency call to arrival at patient' characteristic which had previously operated on a median of 18 minutes.

The difference in operation between these two tasking epochs is reflected in publications describing system performance in case identification of severe paediatric trauma cases. In a study comparing standard ambulance service dispatch to HIRT-system performance, the latter identified more than six times as many severe paediatric trauma cases when in operation alongside the standard ambulance tasking system.[201] When HIRT-team tasking was available the time to arrival at the paediatric trauma centre (PTC) displayed a median of 92 minutes (interquartile range (IQR) 50-261 minutes) compared to when HIRT-team tasking was unavailable where time to the PTC displayed a median of 296 minutes (IQR 84-583 minutes).

A subsequent study comparing system performance before and after disruption of the HIRT-team tasking system focussing on the paediatric trauma system showed that successful case identification rates of severe paediatric trauma fell from 62% to 31% when the existing HIRT system was discontinued.[202] With this change in tasking approach, the median time to arrival at the PTC increased from a median of 69 minutes (IQR 52-104 mins) to 97 minutes (IQR 56-305 mins). While these studies focus on paediatric tasking there is no reason to suspect that the situation would be any different in tasking for adult patients.

Beyond expanding the permitted time between time of injury and application of NIRS oximetry monitoring from 30 minutes to 45 minutes, there were no other available approaches to optimise study subject recruitment.

Impact on Intended Studies

These imposed changes therefore significantly altered the trajectory of this project. The intended study to assess feasibility of prehospital cerebral oximetry was able to proceed much as intended with a total of 63 subjects included for analysis. However the time taken to recruit this many subjects was significantly expanded.

This reduction in recruitment rates then impacted more significantly on the other components of the project. After 4 years of subject recruitment, the total number of subjects available for analysis amounted to 79. At this point the only reasonable approach was to undertake analysis utilising available data to act as a pilot observational to inform further understanding.

Feasibility of Prehospital Cerebral Oximetry

This study demonstrated that NIRS cerebral oximetry was capable of obtaining monitoring data for time periods in keeping with other physiological monitors already in use. With a monitoring set-up requiring application of three optodes, the median percentage of prehospital time monitored in at least two functional sensors was 91% and all three sensors provided adequate monitoring characteristics 71.4% of the total monitored time. In 76.2% of subjects, both cerebral sensors

provided data (45 patients with all 3 sensors providing adequate data and 3 of 12 patients in the '2 sensors adequate' group being adequate bilateral cerebral monitoring).

At the same time, within this research model, there was no difference observed in either time spent at the accident scene or total prehospital time when patients had cerebral oximetry compared to those occasions where patients were excluded on the basis of identifiable criteria at the accident scene, or those occasions where no study observer was available but the patient otherwise met criteria for inclusion.

This work represents a key hurdle in the consideration of further exploration of the role of NIRS cerebral oximetry in the prehospital trauma setting. The cut-off requirement for > 70% of possible prehospital monitoring time demonstrating successful data capture was set as a pragmatic benchmark. This was after internal review of the performance of other monitors used in our prehospital context (pulse oximetry and electrocardiograph). In earlier work in volunteers placed in outdoors environments and then through a phase of ambulance and helicopter transport we were able to establish that NIRS cerebral oximetry monitoring was feasible in a controlled setting, although the majority of interruptions to monitor signal during helicopter transport were noted to be on the side of the forehead most exposed to ambient light through the aircraft window.[3]

There is a recent publication reporting on feasibility of NIRS data collection in the context of multicentre post-cardiac arrest research that set a target of $\geq$ 80% of monitoring time in the considerably more controlled hospital environment.[203] This work was to establish feasibility of this NIRS data capture for a future study of cerebral autoregulation and optimal mean arterial pressure in patients with hypoxic-ischaemic brain injury after cardiac arrest. This team was able to capture bifrontal NIRS measurements for 96% of total monitored time, noting that the in-hospital

monitoring duration was substantially longer than in prehospital care, with a median of 47.5 hours of monitoring time. The defined set-point for acceptable data capture to proceed to further investigation supports the position that our pragmatic cut-off of $\geq$ 70% of prehospital time being monitored is reasonable.

Recently other reports have been published of use of NIRS cerebral oximetry in prehospital contexts including in the care of out-of-hospital cardiac arrest patients and in the context of prehospital anaesthesia and intubation.[204–207] One of these studies, a prospective observational series evaluating cerebral desaturation events around the time of prehospital anaesthesia and intubation reported on the proportion of artefact-free monitoring time with a rate of 94.5% of the total monitoring time.[207] This work involved application of a single left forehead sensor by the clinical team, who were instructed not to act on any NIRS oximetry values. Amongst the exclusion criteria were any physical barriers to application of the sensor (e.g. forehead laceration) and the treating team indicating that workload was “too high to ensure standard levels of clinical care at the time of recruiting”. There is no indication as to how a monitoring signal was defined as being free of any artifact. The other available reports do not comment on success of signal capture.

Within the context of our study, a dedicated study observer was responsible for initiating monitoring as soon as possible after arrival at the patient and then for maintaining vigilance that monitoring signal was still being obtained. This measure was taken to ensure that there was no interference with the usual duties of the clinical team in their care. Similarly the device used was the Nonin EQUANOX 7610 Regional Oximetry monitor (Nonin^{TM}) which is equivalent to the commercially available Nonin EQUANOX 7600 model monitor but with a connection to a standard portable computer. No values were displayed on the screen for any monitored variable. Each

channel in use displayed only confirmation that the NIRS monitoring signal was being captured. This was presented as “Sensor OK” or alternatively “Check Sensor” where there was an issue along with a secondary screen display flagging issues with sensor contact where relevant (displayed as “OOT SSNA” when measurements were “Out of Track” due to a sensor issue).There was also a separate visual confirmation marker confirming values were being written to the record.

While this study procedure does not replicate what would be the usual arrangement where the treating team were also required to manage the monitor and interpret values, it was a necessary precaution to ensure patients received their usual care. This blinding ensured that clinical teams were in no way encouraged to act on rSO_2 measurements at a time where we are still defining what those values might mean and how a clinician should respond. There is a risk that as pragmatic as the study was designed to be, having a designated study observer role reduces the applicability of the findings to clinical practice.

There are pros and cons to establishing a pragmatic benchmark for acceptable monitoring. The risk created is that gaps in data acquisition by interruptions to monitoring signal may compromise the ability to detect associations between rSO_2 and patient outcome or to discern useful monitoring patterns within the other exploratory analysis. The other side of that case is that exclusion of records with gaps in the data acquisition would misrepresent what can be inferred from rSO_2 or HbT values. For subsequent analysis of the prospective study, retaining only records with no interruptions would not reflect what a clinician could achieve at the accident scene. The reality in prehospital medicine is that there will be interruptions to monitoring. Any association needs to be clear enough between rSO_2 and patient outcome that displayed values at the accident scene truly contain meaning and justify a clinical response.

Exploring Associations Between Cerebral Oximetry and Patient Outcomes

Any association between prehospital cerebral desaturation as indicated by rSO_2 and patient outcome would offer information not previously available to the prehospital clinician. It would offer prognostic information at a minimum. It may have the effect of influencing subsequent hospital care as an early indication of significant cerebral injury or compromise in a specific area could increase the focus on early cerebral imaging and intervention rather than dealing with other issues. This situation is analogous to the utility of point-of-care ultrasound in the prehospital setting providing assistance with diagnosis that the prehospital clinician may not act on themselves but which can expedite subsequent prioritisation of care in the hospital.[208]

If there was an association between prehospital cerebral desaturation and patient outcome it would be reasonable to consider following algorithms aimed to ensure the maximum probability of providing adequate blood flow and oxygenation to cerebral tissue in much the same way as similar suggestions have been made in the cardiac surgery setting.[149]

In our study we were unable to demonstrate any association between cerebral desaturation, defined as StO_2 below 45% for 1 minute or more, and either long-term functional outcome as measured by GOSE at both 6-month and 12-month intervals, or patient mortality. 79 patients in were in the final analysis, with 14 patients in the abnormal NIRS group. There was no difference in the proportion of brain injury deaths between patients with abnormal NIRS (14.3%) and normal NIRS (6.2%; $p = 0.287$). Likewise although the relative risk (95%CI) of death associated with

abnormal NIRS at 24h, 30-days, 6-months and at 12 months postinjury were 4.64 (95% CI: 0.31-69.85). 2.32 (95% CI: 0.47-11.45), 2.29 (95% CI: 0.46-11.27 and 2.14 (95% CI: 0.43-10.56) respectively the range of the relevant confidence intervals is such that an association is not confirmed.

The study did show that those with severe traumatic injuries had a RR of death of 17.97 (95% CI: 1.13 to 286.60) and those with severe traumatic brain injuries had a RR of death of 62.21 (95% CI: 3.9 to 992.91). In terms of other short-term outcomes, there was no difference in the distribution of first CT and worst CT Marshall scores on the basis of NIRS grouping.

There was no difference in proportion of patients with poor recovery at either 6-months or 12-months post-injury in patients in the abnormal NIRS group vs normal NIRS group. Again, there was a strong association between either severe brain injury or severe traumatic injury with poor functional outcome at 6- months and 12-months post-injury.

One explanation for the inability to demonstrate a meaningful relationship between cerebral desaturation and patient outcome is the limited sample size of this study. This project operated as a pilot study with a prospective observational design. During the initial stages of recruitment the centralised tasking authority changed their approach to allocating advanced EMS resources. Rather than allocation of the resource on the basis of likely time to reach the patient, a geographical boundary was used to allocate medical assets. This resulted in a profound decrease in tasking of the CareFlight prehospital team and therefore a significant impact on the available study sample. Recruitment was terminated to facilitate analysis and further planning as appropriate. The sample size in this project is similar to other pilot studies in the prehospital field. Nurmi *et al* in their prospective pilot study examining cerebral desaturation events around intubation included 83

patients for analysis and Sakai *et al* as well as Prosen *et al*, studying prehospital application for patients undergoing cardiopulmonary resuscitation, included 87 patients and 53 patients respectively.[206,207,209] Only the study in out-of-hospital cardiac arrest by Genbrugge *et al* is significantly larger, with 329 study subjects included.[210] With significant challenges in recruiting study subjects in the subset of prehospital patients for whom a physician-paramedic EMS team is activated, the sample size is reasonable in a pilot study context but is likely to be inadequately powered to demonstrate even simple associations between cerebral desaturation and patient outcomes.

A further potential explanation relates to the originally defined cut-off point to define normal vs abnormal NIRS. Abnormal NIRS was defined as $rSO_2 \leq 45\%$ for ≥ 1 minute. This initial element of the study design was based on available work at the time associating outcome with cerebral desaturation, though in the setting of paediatric heart surgery.[211] There has been little published since that time to establish an agreed definition for a significant cerebral desaturation event.

Reviews in the area suggest a generally agreed range of normal rSO_2 being 55-75% across a range of neonatal, paediatric and adult settings.[212] There is less clarity as to where a clinically relevant threshold should be set for cerebral desaturation. In the pilot study by Nurmi *et al*, the primary definition used was $rSO_2 < 50\%$ for ≥ 5 minutes.[207] However the authors note that there remains a lack of clarity as to what the appropriate threshold should be and tested a variety of definitions. We utilised the rSO_2 threshold of 45% with a timeframe of any period longer than a minute to ensure that events with low saturation were captured within the analysis. It is possible that defining a longer period of desaturation as a necessary condition would ensure all those considered in the abnormal NIRS group were more likely to have clinically significant desaturation but would also require an even larger sample size to be likely to establish any association. Unlike

the work by Slater *et al*, there is no work to establish a "desaturation dose" in the setting of trauma or TBI that includes both consideration of the degree of desaturation and the duration of exposure.[150]

There is one prospective series with 61 adult patients in whom optodes could be applied that suggests early values of rSO_2 may have some prognostic value for hospital mortality.[213] Those who survived to discharge expressed higher rSO_2 values at arrival to the operating room than those who did not survive (75.4% +/- 9.8% vs 71.0% +/- 20.5%; p = 0.013). A similar association was noted at measurement 1 hour after admission to the intensive care unit (ICU) (74.7% +/- 1.5% vs 61.9% +/- 19.4%; p = 0.029) though not immediately after the operation or at 24 hours in ICU. However the group is only able to describe the implications of this finding as a suggestion that borderline rSO_2 values may have prognostic value and be independently valuable. The authors do not suggest a specific cut-off point that can be used as a threshold.

Recent reviews reinforce this lack of defined thresholds while highlighting that while there is a general picture of rSO_2 being inversely associated with increasing ICP, correlation with measures such as SjO_2 and $P_{bt}O_2$ are highly variable .[214,215] At this time it would seem there is still not enough information derived from large studies to establish whether there is a threshold cut-off for rSO_2 that could be utilised as a guide for further prehospital research. There is likewise no relevant desaturation dose taking into account duration and size of rSO_2 reduction that could be utilised in a similar fashion.

Even were such a cut-off or desaturation dose established it is important to note that these values could only be relied upon if the device subsequently used was the same as the monitor used to derive those values. This problem arises from the degree of variance seen in the displayed results,

a form of interindividual variability between machines, arising from the hidden but different algorithmic approaches employed by manufacturers.

A final and significant factor challenging the ability to establish associations relates to the proportion of monitoring time with successful data capture. As described above, a cut-off for proportion of monitored time of > 70% of total prehospital time was established and is in keeping with another technical feasibility study.[203,216] This benchmark is reflective of real world experience in prehospital medicine where interruptions to monitoring are an issue more often than in hospital settings. However it does allow for significant windows of time where cerebral oximetry data is not captured. This introduces a possibility of missed desaturation that cannot be quantified.

In summary this analysis follows on from the technical feasibility work. It suggests that in a research structure designed pragmatically to replicate real world clinical experience of monitor performance, there was not an evident association between NIRS cerebral oximetry values and patient outcomes. These outcomes included functional outcome at 6 months and 12 months, along with patient mortality. As a pilot study this may be a function of inadequate power to detect a difference. However the combination of persisting uncertainty over clinically relevant desaturation dose thresholds along with intra- and interindividual variability of device performance and the issue of inevitable interruptions in monitoring all challenge the ability of NIRS to provide early prognostication utilising this approach to analysis.

Testing New Methods of Analysis of Cerebral Oximetry

This element of the study utilised the existing NIRS oximetry data and applied three different analyses. The first of these could be considered as a standard statistical analysis. The second applied machine learning after feature extraction directed by the research team on the basis of existing literature. The third approach involved application of a convolutional neural network (CNN), a deep learning approach that is an end-to-end learning method. This means that the CNN itself defines and extracts relevant features, rather than this being a manual process. The second and third components of this analysis represent the novel analysis techniques first envisioned in the original ideal study protocol.

For both the statistical analysis and the simple machine learning approach, there was no significant association or predictive ability demonstrated linking either rSO_2 or HbI to the relevant clinical outcomes of GCS < 12, AIS (Head and Neck) $\geq$ 3 or patient mortality at 30 days.

However the CNN approach showed improved precision and accuracy when interrogating rSO_2 and HbI in both channel 1 and 2 with respect to GCS < 12, AIS Head and Neck $\geq$ 3. For Channel 1 there was also some predictive ability demonstrated for mortality at 30 days despite the limited number of results in this grouping. The CNN approach also facilitates pattern recognition across more than one channel at a time, with analysis involving fusion of rSO_2, HbI, oxyhaemoglobin and deoxyhaemoglobin improving performance of the model across outcomes and in both channels.

This component of the thesis is an effort to explore the possibility that clinical utilisation of NIRS cerebral oximetry may be possible if analysis incorporating pattern recognition approaches

developed through machine learning or deep learning techniques could be incorporated into interrogation of the NIRS data outputs. If such associations were established, pattern recognition could be built into monitors to alert clinicians of evolving changes or the breach of critical thresholds or cumulative values. Meaningful predictions based on DL-defined features warranting extraction could also provide guidance as to which critical parameters are worthy of further focus or which measurements may be suitable for the development of correlation indices that could prove useful to the clinician.

The underlying rationale for attempting a different approach arises from a number of observations:

- The demonstration of associations between reduced rSO_2 and adverse patient outcomes have not, to date, led to any change in patient outcome when treatment algorithms to optimise rSO_2 alone are incorporated into care.
- NIRS-derived cerebral oximetry does not currently provide absolute values and is likely to be more appropriately used as a trend monitor.
- Analysis reliant on rSO_2 thresholds or fixed cut-offs without being able to reliably highlight cumulative time, repeated breaches in thresholds, or patterns associated with evolving pathology may represent analysis that starts when an endpoint of desaturation is reached, rather than highlighting a trend that would allow a clinician to intervene before cerebral desaturation is established.
- Work exploring the contribution of NIRS cerebral oximetry to indices related to cerebrovascular reactivity suggests that NIRS signals may need to be coupled to other measured parameters to understand dynamic physiology that clinicians can then act upon.

The first of these observations may be in part due to the difficulty in discerning which of the numerous elements contributing to the observed end-point of decreased rSO_2 might be the primary problem to address. The range of potential culprits is wide. Any issue with oxygenation may be a significant causative factor. Where there is reduced delivery of blood flow into a region, whether due to generalised hypotension or limitations of CBF due to factors such as raised ICP or cerebral vasoconstriction caused by hypocapnia, rSO_2 can be expected to decrease. A collection of blood producing an altered reading or cerebral oedema causing slowed diffusion into an area beneath the optode may also directly impact rSO_2 values.

The other observations highlight that for NIRS cerebral oximetry to become useful in a prehospital context or in critical care settings where the aim is to respond within a time-critical window for the patient, a key requirement will be the need to rapidly identify trends, thresholds or patterns that may not be apparent to the clinician's eye. There may also be a need to be able to simultaneously consider trends in NIRS parameters such as rSO_2 and HbI against simultaneous physiological measurements such as blood pressure or indeed across multiple NIRS optodes.

We therefore undertook exploratory analysis of key NIRS-oximetry variables, rSO_2 and HbT (labelled within the EQUANOX system as HbI) against the patient outcomes of mortality at 30 days, first GCS < 12 as a clinical marker of significant head injury, and AIS (head and neck) $\geq$ 3. Analysis utilising the three approaches, a standard statistical approach, simple machine learning approach with manual data extraction, and an end-to-end deep learning approach suggested that the CNN approach was able to demonstrate a predictive ability with precision and accuracy where other forms of analysis could not.

The outcomes of GCS < 12 and AIS (head) $\geq$ 3 were chosen as outcome variables as both should be associated with significant TBI. These subjects therefore represent the patient groups most likely to show evidence of a change in measured physiology. The two initial approaches to analysis did not indicate that NIRS cerebral oximetry revealed altered physiology or detected an injury. The AIS (head) $\geq$ 3 group incorporates a larger group of patients than the GCS < 12 group and includes patients with a variety of pathologies on first cerebral imaging after arrival at the hospital including subdural haematoma, traumatic SAH and intracerebral haemorrhage yet no association could be demonstrated using these methods. The suggestion that the CNN approach was able to provide recognition of patterns with improving precision and accuracy, particularly on fusion of multiple measurements including the additional data streams correlating with oxygenated haemoglobin and deoxygenated haemoglobin, is of considerable interest.

Over the time of work on this thesis there has been relatively little advance in the clinical use of NIRS tissue oximetry in either prehospital medicine or TBI care in the hospital. In prehospital medicine the most recent additions to the literature have been in the area of out-of-hospital cardiac arrest and as part of a pilot study in the context of prehospital anaesthesia and intubation with these published works still focussed on the single parameter of rSO_2.[204,207,209,217] The last of these studies was not powered to show associations between rSO_2 and outcomes. In the context of out-of-hospital cardiac arrest, studies to date have suggested that return of spontaneous circulation is associated with a pattern of increased rSO_2 but there is no evident association with eventual survival to discharge. In essence this merely demonstrates that as the circulation returns, oxygenation and perfusion resume in the tissues. Confirmation of resumption of circulation does not equate to providing new information not available via other existing monitors that would then help the practitioner alter treatment to optimise cerebral perfusion. More information is required of the monitor to change patient outcomes.

There has been some further interest in the use of NIRS systems to discern a difference between cerebral hemispheres as a way of detecting intracranial blood collections. These devices provide comparisons of signal over scanned areas rather than focusing on metrics associated with oxygenation or perfusion. Descriptions of use of these devices for intracranial haematoma detection have noted significant issues with accuracy and even recently Schober *et al* reported 12 of 17 volunteers had a measurement suggesting haematoma, a false positive rate of 70.6%.[218] In a review published in 2017, Brogan *et al* reported a cross-study sensitivity of 78%, specificity of 90%, positive predictive value (PPV) of 77% and negative predictive value (NPV) of 90%) and suggested available technology does not meet the standards required of a diagnostic or triage tool. A similar review by Viderman *et al* summarises the figures reported across available studies showing a wide range of performance in studies since 2006.[219]The reported ranges are sensitivity ranging from 58.5-100%, specificity ranging from 42.9-100%, PPV of 10.8-93.5% and NPV of 35.7-100%. The description of current utility remains that NIRS “may be of use”. This is even more evident when taking into account that some recent studies report rates of inability to evaluate a suggested lobe of the brain of up to 33.9% of total scanning locations.[220]

There has been further development of NIRS-derived indices as part of assessment of cerebrovascular reactivity during the course of this thesis. If use of this technology matured to the point where impaired cerebral autoregulation could be inferred or optimal levels of CPP and MAP could be discerned this would offer clinicians meaningful new information to help target their therapy. NIRS-derived THx appears to show moderate to strong correlations with PRx.[214] The same is true of TOx and both PRx and Mx. Rivera-Lara *et al* reported on a prospective study of 91 comatose patients in which it was possible to calculate optimal mean arterial blood pressure in 97% of patients.[221] They also found on multivariate proportional hazard analysis that duration

outside the optimal mean arterial blood pressure range for more than 80% of monitoring time, along with absolute difference between clinically observed mean arterial blood pressure and optimal mean arterial blood pressure of > 10 mmHg were factors independently associated with mortality at 3 months. An ability to define optimal mean arterial blood pressure for each patient would be a huge advance for clinicians.

These positive steps and demonstrated associations still leave much work to be done. Indeed, recent published work reporting on a Delphi consensus approach to reflect current knowledge of cerebral autoregulation, incorporation into TBI management and research priorities noted the complexity of the available measurements and that there was no consensus on how these measurements should be used in clinical practice, whether they were sufficiently accurate, reproducible or displayed validity[222]. There was also no consensus possible on whether cerebral autoregulation status could be safely implemented in clinical care. There remains a lack of clear level I evidence that clinical treatment algorithms responsive to autoregulation indices lead to improved outcomes.[223] As a result there is considerably variability in use of cerebral autoregulation monitoring in neurocritical care and a range of views on whether it is reasonable to proceed to randomised controlled trials incorporating such measurements or whether further associations should be established first.[224]

There are additional significant caveats for prehospital application of any of the promising developments bringing measurement of cerebrovascular reactivity or the derivation of optimal perfusion pressure to the bedside. These indices frequently require measurements less often included in care at the side of the road, such as invasive arterial blood pressure or transcranial Doppler ultrasound. Otherwise they require interventions not undertaken in prehospital settings such as insertion of a form of ICP monitoring.

The other key component of successful measurement of indices is time with utilised monitoring windows of at least 30-60 minutes.[164] The example of CPP_{OPT} has been shown to take around 5 hours before producing output values.[225] These timeframes represent the entirety of the prehospital monitoring time or even well beyond the hypothetical arrival at hospital of the EMS crew transporting their critically ill patient.

This 'time to meaningful information' problem, that impacts utility for the clinician, is also starting to be addressed in ways that indicate that analysis of rSO_2 in isolation may not be the solution. There has been recent progress with a cotrending approach that compares the relationship between instantaneous rSO_2 to MAP, initially reported as a part of a retrospective analysis of data obtained in the context of cardiac surgery utilising cardiopulmonary bypass.[226] The cotrending method uses windows of data with a duration of only 50 seconds which are then utilised to facilitate comparisons of the gradients between MAP and rSO_2 signals. Where there is similarity between the gradients, this suggest a pressure-passive CBF state has been reached where cerebral autoregulation is impaired. Utilising a TCD-derived lower limit of autoregulation, the cotrending method exhibited limits of agreement around 10 mmHg and provided outputs describing cerebral autoregulation in 63 seconds. Novel approaches therefore continue to be developed that may allow real-time action by clinicians, although still with a need for invasive monitoring in this instance.

The current state of play is that non-invasive cerebral oximetry has not become part of established clinical practice of TBI management in either the prehospital or hospital setting. In updated prehospital TBI guidelines there has been a shift upwards in the suggested systolic blood pressure targets across age groups with the most recent suggestion being that adults should have a systolic

blood pressure of 110 mmHg and above on the basis of recent publications suggesting that for adults the systolic blood pressure range associated with the lowest risk of mortality is 130-180 mmHg.[227,228] Cerebral oximetry is not mentioned in the prehospital guidelines.

Updated guidelines for hospital care also do not define a significant role for NIRS. Maintenance of SjO_2 at a level of 50% or higher is the only updated recommendation relevant to cerebral oximetry in the most recent edition.[229] These guidelines also suggested a higher systolic blood pressure target of $\geq$ 110 mmHg in the 15-49 year old age group due to evidence that a higher target blood pressure may be beneficial.

The lack of progress with NIRS oximetry to provide clear cut-offs or additional information to guide treatment in real time suggests there is still a need to broaden efforts to find a useful approach. The suggestion that a CNN approach may be able to establish a means of interrogating NIRS oximetry data at a level hidden to the clinician's eye and yet linked to meaningful patient outcomes is a novel and potentially important finding. There is value in at least exploring approaches that facilitate rapid derivation of useful information by a deep learning model that can recognise patterns contained entirely within the rSO_2 and HbT signals.

There may be further potential to also incorporate additional signals from non-invasive sources such as the perfusion index from peripheral pulse plethysmography. The capacity of the CNN model to facilitate a fusion step where the end-to-end learning is facilitated across multiple signals simultaneously is a unique property of this deep learning approach.

The ideal end-state for incorporation of NIRS cerebral oximetry into clinical care is to be able to rapidly and reliably analyse evolving trends and patterns linked to patient physiology across

multiple detected parameters in real time. The CNN approach may represent a technique to accomplish this. Commencing exploration of novel analysis approaches to unlock the potential of NIRS oximetry was the purpose of this arm of the pilot study.

Although the predictive ability of the CNN approach offers some cause for optimism there are significant caveats with deep learning methodologies. It is critical that clinicians understand the nature of the analysis and the linked assumptions and potential issues in the same way that the wrinkles in other analysis methodologies are already understood. The CNN approach offers unique solutions but comes with specific challenges in training of the system and interpretation of the results.

The first critical element relates to the nature of an end-to-end learning process. This is distinct from the machine learning approach, where the system is manually directed to the features on which it must base its learning. The CNN approach defines its own features and generates a result. While the result may produce precision and accuracy that are promising or be able to generate a result where simple machine learning fails, such as in the mortality at 30 days outcome in our work, the specific features that the CNN has chosen for extraction and learning are initially hidden to the external viewer.

In a simple machine learning system the analysis is linked to chosen inputs and therefore the association with clinical parameters or physiology is known. However the results from the CNN approach cannot be assumed to be directly linked to extraction of expected clinical features. There is therefore a requirement for an additional post-processing step to better understand the selected features. This can be done with a variety of explainable artificial intelligence (XAI) techniques. Methods such as layer-wise relevance propagation, saliency maps, and gradient-based attribution

techniques aid interpretability by highlighting relevant regions in input signal or identifying influential neurons within the network.[230] When applied to CNNs these methodologies make their operation more transparent and understandable and enhance trust in the CNN-based models. The post-processing application of XAI techniques also facilitates the engagement of domain experts to validate the decisions made by the model, identify any biases and improve model performance and generalisability.

The requirement for this additional post-processing step can, however, generate its own enquiry. Where the CNN has applied a focus to specific features, this may be used as a prompt to centre further investigation on the same feature. Whereas that feature may have remained hidden to the clinician or researcher, or only been uncovered after multiple cycles of investigation undertaken over a longer period of time, the application of DL can potentially more efficiently highlight the measurements that matter.

It is also the case that DL approaches such as this require ongoing training and validation with much larger datasets. While this work hints at the possibility that DL techniques can demonstrate predictive ability with limited datasets, it is important to note that the further validation with larger datasets is explicitly required to ensure that the observed results are not created by the overall lack of study subjects recruited. Limitations in our dataset may create commonalities across all the analysis techniques selected. For statistical analysis, the number of subjects itself likely results in insufficient power to establish an association. For ML some extracted features had minimal data points and this limited their ability to add to the predictive ability of this approach. The issue of limited data is partly offset by the inclusion of a proportion of patients with significant TBI in whom it would be reasonable to expected altered NIRS oximetry signals.

While the small number of total subjects significantly limited the available data, a more significant contributor to the challenges inherent in a small dataset in our case may be the significant windows of the time series where there was no measurement. These gaps in the monitoring data, while within the reasonable requirements of technical feasibility, represent large sections that are unavailable for statistical analysis but also not available for feature extraction under ML or DL approaches in either the training or validation sets. All time points with no available data act as null value sectors that limit analysis. Each time monitoring values were established, the initial 20 seconds was treated as a missing value to allow for steady sampling to be guaranteed. This is necessary but further limits the performance of ML and DL models. The practical factors relating to the success of monitoring are significant hurdles to overcome to facilitate proper exploration of this approach.

This work therefore describes a novel approach to monitoring NIRS signals that hints at the potential of DL approaches to identify patterns that are otherwise hidden within the monitoring signal. Further work to confirm the value of this approach requires larger datasets, a process critically dependent on both increased numbers of subjects and more successful data capture through improvements in monitor performance. There is also a need to undertake post-processing evaluation involving the application of XAI techniques to better understand the features selected by the CNN and evaluate their clinical relevance and generalizability.

However where standard approaches yielded no clinically useful associations, our novel approach may be the basis for a pattern recognition approach that can be built back into monitors and thus provide real-time flagging of clinically meaningful changes in patient condition.

Conclusions And Future Directions

The work described in this thesis explores the potential for a non-invasive monitoring device to provide physiological measurements with clinical relevance for TBI patients being cared for in the prehospital environment. It arises from a background understanding that TBI remains a major health issue with profound implications for individuals and society and that finding ways to improve outcomes must be a high priority area.

Initially significant work was undertaken to confirm technical feasibility of this project. We were unable to demonstrate any form of association between NIRS-derived cerebral oximetry utilising standard analysis approaches. However application of a DL approach incorporating a CNN developed precision and accuracy that suggests there is value in pursuing novel analysis techniques. The combination of negative findings in the context of standard analysis approaches and the promise suggested by DL allows for a range of suggestions that can guide future endeavours in the area of NIRS and TBI. There remains the potential to develop meaningful approaches to incorporate tissue oximetry into TBI care in both the prehospital and hospital environment.

Suggestion 1: Available NIRS Oximetry Monitors Require Further Improvement

A significant contributor to the difficulties of data acquisition for this project was related to the available technology. Establishing processes to optimise the likelihood of technical feasibility as a component of this research required around two years of effort, including development of research procedures for study observers dictating optode positioning, securement and shielding. This was necessary particularly to ensure sensor contact and exclusion of external sources of light.

The combination of this effort and a dedicated team member to maintain monitoring allowed for benchmark technical feasibility to be reached. However substantial gaps in monitoring remained and this was a substantial issue when seeking to analyse the data utilising all the methods described. Although as a pilot study, even one including a significant proportion of patients with significant head injuries, it may not have been possible to demonstrate associations utilising standard statistical approaches, periods of artefact or absent monitoring made the likelihood even lower.

To meet the ideal of a portable, non-invasive monitor delivering high resolution physiological information with considerable accuracy there is a need for further improvements in engineering. Further research before those advances occur appears likely to result in incomplete monitoring samples that may limit analysis to measurements principally related to rSO_2. Any research with a focus purely on rSO_2 values seems unlikely to highlight clinically useful applications of noninvasive cerebral oximetry. There is already some literature with a focus on rSO_2 values in the prehospital environment. At most this confirms that circulation is occurring or may eventually lead to a gross association of low rSO_2 with bad patient outcome. Confirmation of observed physiology does not translate into information that allows a clinician to intervene effectively. The observation that the DL approach offers promise stresses that reliable and highly accurate data acquisition is required to undertake more nuanced approaches to data analysis. It is these nuanced approaches that seem more likely to detect meaningful physiological trends incorporating multiple monitoring inputs to alert clinicians to changing patient status.

There is some evidence of further evolution of NIRS monitors. The Dutch Helicopter Emergency Medical Service have reported initial exploration of use of a wearable matchbox-sized NIRS device for measuring somatic oximetry values that was originally designed for athletes.[231] Advances to

decrease the size of the monitoring device is welcome. At the time of commencing this thesis project there was a single device on the market that could be considered portable and able to withstand the robust prehospital environment which made it the default choice for our research. Devices designed to function in environments more challenging than the hospital are welcome but this is not the only area requiring improvement.

A range of other relevant limitations in commercially available NIRS oximetry devices were noted in a scoping review of cerebrovascular reactivity indices by Sainbhi *et al*.[232] Commercial devices have limited channel capacity which impedes spatial resolution in particular.[233] Monitoring systems that can increase both spatial and temporal resolution as a result of increasing the measurement frequency up to 250 Hz at multiple channels are available in the research setting and represent a significant advance.[234–238] However those advances have not reached the bedside and are certainly not ready for the prehospital environment, whether in research or as a tool for the clinician.

For prehospital settings, further work is therefore required to make sure NIRS monitors are lightweight and rugged, but more importantly that there are advances to ensure adequate protection from ambient light without the need for additional shielding beyond the sensor, consistent optode contact without disturbance and enhanced spatial and time resolution through improved channel capabilities.

Without these advances the scope to move beyond the crude sketch of rSO_2 alone will remain limited.

Suggestion 2: Agreed Standards and Open Access in NIRS Oximetry Would Assist Clinicians and Researchers

For most physiological monitors in use for clinical care and research, the underlying technology is essentially identical and nomenclature is consistent. This allows easy and direct comparison from device to device and an ability to extrapolate findings from one study exploring that monitoring methodology to another using the same class of monitor.

This is not the case for NIRS. While all commercial manufacturers display some form of metric that represents tissue oxygen saturation, the ascribed name might be rSO_2, StO_2, $rScO_2$ or TOI. There is also variance on concepts such as HbI or HbT, the measure reflecting total Hb in the sampled area. This does not enhance clinical care or understanding and an agreed standard, unless the underlying optics approach is entirely different, would be useful.

An even more significant issue is the utilisation of varying algorithms to arrive at measurements.[239] As mentioned earlier in this thesis each manufacturer utilises their own algorithm to process data and assumptions utilised within that algorithm can profoundly influence the displayed value. The effect of this is that even if this research had demonstrated associations it would only be possible to have confidence that there was a demonstrable association with the Nonin EQUANOX monitor. Similarly any future findings on generations of research monitor with vastly different measurement characteristics for rSO_2 may not necessarily provide evidence that NIRS oximetry values using a simpler commercial version would be linked to the machine that generated the research evidence.

Although this issue has been flagged by a range of authors, history may be repeating as commercial manufacturers seek to embed measures of autoregulation into their tissue oximetry devices. If future devices incorporate a variety of measures purporting to indicate cerebrovascular reactivity but utilise their own nomenclature built from input parameters already displaying their trademarked measurement names and with opaque algorithms layered on top of already hidden calculations the problems will multiply. All research undertaken with the commercial monitors will be compromised by an inability to undertake direct comparisons between devices or even to confidently assert what they are measuring.

The optimal outcome for clinicians and researchers would be to strive for agreement on the gold standard approach to generating NIRS oximetry monitoring data and have manufacturers adopt a single approach. This seems unlikely to occur.

A reasonable alternative would be to reach an agreement that any research utilising a monitor should link to technical specifications for that device including the precise method of measurement and the assumptions in the algorithm underpinning calculations. This open access approach would allow work to be done to establish how different algorithms relate to each other and therefore what correction factors might be required when displaying ‘absolute’ values.

Clinicians and researchers could then evaluate whether published evidence from a particular source translates well to their setting and might be useful for their own projects or to add to clinical care.

Suggestion 3: Further Hospital-Based Research Should Define the Measurements that Matter Prior to Further Prehospital Research

The prehospital setting is a distinct clinical environment. The clinicians who attend accidents have specific skillsets unique to that setting and patients receive care at a very different point in their clinical condition. The initial physiological responses after injury can alter substantially in the time leading up to arrival at a hospital and may not be seen again through their illness.

Prehospital medicine therefore requires research specific to its setting. It should not be assumed that observations in physiological parameters at the hospital will replicate what would have been the case in the prehospital setting, even where the patient might seem to be in a similar clinical state. Hospital research should in no way be assumed to replicate prehospital medicine.

However the prehospital setting also does not have as robust a research infrastructure as hospital medicine. This places more pressure on designing studies optimally up front. There are a number of variables outside the control of a researcher that can nevertheless significantly impact on their work. As an example, during the life of our pilot study the centralised tasking approaches in the Sydney metropolitan area that determine patient load were redrawn. The result was tasking with geography as the prime determinant of response rather than tasking the advanced EMS team most likely to reach the patient as quickly as possible.[202] This led to a significant decrease in the volume of work with a direct impact on recruitment. Coupled with the challenges of establishing research procedures within the chaotic environment of an accident scene, exploratory research can be very difficult.

In the context of NIRS oximetry progress has been slow even in well-resourced hospital settings. While it may have been assumed that across the period of this project there would be a substantial increase in clarity as to how best to interpret noninvasive cerebral oximetry in a variety of clinical settings, and what specific treatments should be prompted by abnormal values, this area is still one of uncertainty.

To optimise the likelihood that research directed at the moments after injury is focussed on the right NIRS oximetry parameters, includes the right comparators to derive relevant indices, and incorporates an analysis approach linked to meaningful physiological changes there is a need for further work to define the measurements that matter. This can clarify whether the best focus should be on a single value, such as either rSO_2 or HbT, or a combination of these and other measurements contained within the NIRS oximetry signal.

Having provided an initial description of the application of a convolutional neural network to analysis of NIRS oximetry measurements, this particular approach is a potentially exciting new path worth further exploration. Within our work this represents the only approach that demonstrated predictive ability linked to significant patient outcomes even with small datasets for training. As a novel approach, this DL analysis is the area most in need of further exploration to define its role. Initially this requires further exploration with much larger datasets generated from larger numbers of patients and consistently captured, long duration NIRS oximetry recordings. Each dataset requires adequate numbers both in the training and validation groups to establish the performance across precision and accuracy. There is also a need to undertake comprehensive post-processing evaluation to confirm extracted features are strongly linked to patient physiology.

This work will also involve assessment of whether additional measurements can inform the DL model as part of fusion of multiple data streams with their own patterns to recognise. Those measurements may be noninvasive, such as peripheral pulse plethysmography. Alternatively invasive measurements, such as arterial blood pressure, may be highly useful as an additional source of physiological data.

Datasets of adequate size to pursue DL approaches comprehensively need to be larger. These systems are best trained with what is colloquially referred to as 'big data'. Such datasets will initially be the domain of hospital-based research.

The same considerations apply to the efforts to define the role of derived indices, particularly those that are linked to cerebrovascular reactivity or optimal perfusion pressures. The cotrending approach described by Montgomery *et al* certainly warrants further exploration. Pursuing both these areas primarily in the prehospital environment would impose substantial constraints on the comprehensive exploration still required to understand which measurements matter.

Optimal optode placement represents an additional consideration for which further research would be beneficial. Our study design included an optode sampling a peripheral muscle bed in the hope that it would act as a reference allowing comparison between cerebral and peripheral vascular beds as a way of identifying failure of cerebral autoregulation. An ability to identify the pressure passive brain where failed cerebral autoregulation means that fluctuations in systemic blood pressure were directly experienced by cerebral tissues would prompt a particular emphasis on stability of MAP management and even more judicious avoidance of episodes of hypotension. Optode placement itself may therefore open up whole new avenues to guide clinical decision-making.

There are therefore multiple gaps in our understanding of how best to utilise NIRS cerebral oximetry and how to refine it to measure clinically important physiology. While these can be addressed with further research of sufficient size, even understanding the measurements leaves clinical researchers with an additional area to contemplate. Once the understanding of which measurements matter if established there is a critical additional step required to understand how specific treatment options influence the measured signals and what impact they have on patient outcomes. The clinician is able to alter delivery of oxygen, manipulate CO_2 by altering ventilation, transfuse red cells, administer vasoactive agents to achieve specific targets, and undertake a variety of measures to reduce intracranial pressure. A required element of future research is therefore to develop an understanding of the best use of
NIRS oximetry measurement in the context of how clinicians are manipulating it.

A better grasp of all these elements in the hospital setting would ensure that eventual prehospital research has useful reference points but also that any observational study can be based on confident assessments of how many study subjects will be required to find true associations or to optimise the available training and validation datasets for ML and DL analysis.

The gaps in the prehospital record, the variability of research conditions in the outdoors, and the lack of confidence that we know which measurements matter to lead to an obvious conclusion – the most appropriate way to arrive at good research in the prehospital setting for this particular technology is to address questions more comprehensively inside the walls of the hospital.

Suggestion 4: Prehospital Clinical Use Cannot Be Supported Until These Advances Occur

The commencement of this thesis was accompanied with significant optimism that NIRS cerebral oximetry would provide a clinically useful monitor reliably guiding decision-making to the ultimate benefit of patients. There remain significant questions to answer and whole new areas to explore. That destination has not been reached in either the prehospital or hospital setting.

It is therefore important to explicitly state that NIRS cerebral oximetry should not be a part of prehospital clinical care at this time. In the research setting there should be strict safeguards to ensure that steps are taken to prevent the addition of NIRS monitoring as part of a study imposing any additional burden on clinicians. Although research on cognitive skills and human factors is in its infancy in prehospital medicine, it is the epitome of a cognitively complex environment where the number of pieces of information required by an operator to make a correct decision exceeds the capacity of working human memory. The types of situations where a NIRS cerebral oximeter might be added for observational research purposes are precisely the sorts of clinical cases described in the available research as associated with additional perception of workload in paramedics – high acuity cases such as polytrauma or resuscitation where procedures such as intravenous access or airway management are required.[240] In a setting where qualitative research exploring human factors issues identifies that specific external work environmental challenges include time pressure, mission urgency, icy surfaces or freezing weather, night-time missions, cramped work settings, aggression from family members and intrusive pets, it is vital to ensure the scene is not complicated by factors that only confuse clinical assessment.[241] Indeed the introduction of new guidelines or processes has previously been linked to an increase in adverse events.[242]

This work explores the potential utility of NIRS cerebral oximetry in the prehospital management of TBI. The study design incorporated pragmatic decisions to ensure appropriate blinding and that any observed associations could be reasonably extrapolated to real world clinical use. The combination of challenging recruitment with a small eventual sample size along with gaps in data acquisition made it unlikely that any associations could be demonstrated. However the application of deep learning methodologies to the analysis of obtained measurements demonstrates some promise.

For clinicians and researchers alike this opens up a new area to explore and understand. Machine learning and deep learning require a different understanding of underlying processes in the analysis compared to the standard statistical approaches that are most familiar. The specifics of feature extraction and the differences between a manual process and an end-to-end process in ML compared to DL are highly relevant to understanding how the results link back to true biological changes. There is a need to grasp that when the CNN displays classification results arising from pattern recognition within the system, how it arrived at that position is unknown and further interrogation becomes a necessary next step to ensure there is a meaningful link back to patient physiology. It is a significant shift in approach that is likely to become increasingly relevant for all involved in clinical research.

Our exploratory analysis is a first small step down this road. The next steps require larger datasets, monitors that acquire data more consistently and broader efforts to realise the potential of deep learning. NIRS cerebral oximetry is still some distance from being useful as a prehospital monitor.

Before any efforts to re-explore the utility of prehospital NIRS in the larger scale studies required to establish meaningful associations there is a need for further development of available monitors,

open disclosure of underlying algorithms to allow for informed research, and more academic work in the hospital setting to define the measurements that matter, along with the interventions that might then make a difference. In the interim, NIRS would not be an appropriate addition to prehospital care and should remain a research item only.

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Appendix 1 – Extended Study Subject Hospital Data by NIRS Grouping

	All patients (n=79)	Abnormal NIRS (n=14)	Normal NIRS (n=65)	P value
Mean (SD) ED pulse, bpm[a]	91 (20)	87 (21)	91 (20)	0.497
Median (IQR) ED SpO_2 (%)[a]	99 (97-100)	99 (96-100)	100 (97-100)	0.280
Mean (SD) ED SBP, mmHg[a]	132 (22)	123 (23)	133 (21)	0.142
Mean (SD) ED temperature, °C[b]	36.5 (0.7)	36.3 (0.9)	36.5 (0.6)	0.237
Median (IQR) ED GCS[a]	15 (13-15)	15 (14-15)	15 (13-15)	0.857
ED pupillary reactivity, n (%)				0.360
Neither pupil reactive	4 (5.1)	0 (0.0)	4 (6.2)	
Either pupil reactive	3 (3.8)	0 (0.0)	3 (4.6)	
Both pupils reactive	67 (84.8)	12 (85.7)	55 (84.6)	
No assessment in either or both pupils	5 (6.3)	2 (14.3)	3 (4.6)	
Median (IQR) ED sodium, mmol/L[a]	140 (138-141)	139 (138-142)	140 (139-142)	0.547
Mean (SD) ED potassium, mmol/L[a]	3.9 (0.5)	3.9 (0.6)	3.9 (0.5)	0.712
Mean (SD) ED pH[c]	7.34 (0.06)	7.34 (0.08)	7.34 (0.06)	0.879
Median (IQR) ED PaO_2, mmHg[c]	45.3 (31.2-69.8)	58.4 (40.0-162.0)	44.7 (31.0-65.6)	0.140
Mean (SD) ED $PaCO_2$, mmHg[c]	45.9 (7.7)	46.8 (9.2)	45.7 (7.5)	0.686
Median (IQR) ED FiO_2, (%)[d]	21 (21-21)	21 (21-42)	21 (21-21)	0.609
Median (IQR) ED glucose, mmol/L[b]	7.0 (5.8-8.2)	8.1 (5.9-9.3)	6.8 (5.7-8.1)	0.107
Median (IQR) ED haemoglobin, g/dL[a]	14.2 (13.2-15.2)	13.5 (13.0-14.3)	14.6 (13.3-15.3)	0.136
Median (IQR) ED INR[e]	1.0 (1.0-1.1)	1.1 (1.0-1.1)	1.0 (1.0-1.1)	0.772
Mean (SD) ED creatinine, μmol/L[f]	79.8 (21.6)	82.2 (18.3)	79.4 (22.3)	0.665
Median (IQR) ED HCO_3, mmol/L[g]	24.5 (23.0-26.0)	24.4 (23.2-25.0)	24.6 (23.0-26.0)	0.933
Median (IQR) ED lactate, mmol/L[c]	1.9 (1.3-2.7)	1.9 (1.1-2.7)	1.8 (1.3-2.7)	0.865
ED Pack red blood cells given, n (%)[a]	9 (11.5)	1 (7.7)	8 (12.3)	1.000
ED Platelets given, n (%)[a]	1 (1.3)	0 (0.0)	1 (1.5)	1.000
ED Fresh frozen plasma given, n (%)[a]	6 (7.7)	1 (7.7)	5 (7.7)	1.000
ED Cryoprecipitate given, n (%)[a]	5 (6.4)	0 (0.0)	5 (7.7)	0.583
ED hypertonic solution given, n (%)[a]	4 (5.1)	0 (0.0)	4 (6.2)	1.000
ED inotropes or vasopressors given, n (%)[a]	8 (10.3)	2 (15.4)	6 (9.2)	0.614
ED transfer to destination, n (%)[a]				0.694
Home	3 (3.8)	1 (7.7)	2 (3.1)	
Operating theatres	23 (29.5)	4 (30.8)	19 (29.2)	
Intensive care unit	11 (14.1)	3 (23.1)	8 (12.3)	

High dependency unit	21 (26.9)	3 (23.1)	18 (27.7)	
Ward	20 (25.6)	2 (15.4)	18 (27.7)	
External ventricular drain placed at first operation, n (%)[a]	7 (9.0)	1 (7.7)	6 (9.2)	1.000
Pressure monitor on first operation, n (%)[a]	3 (3.8)	0 (0.0)	3 (4.6)	1.000
Decompressive craniectomy at first operation, n (%)[a]	3 (3.8)	0 (0.0)	3 (4.6)	1.000
Haematoma evacuated at first operation, n (%)[a]	1 (1.3)	0 (0.0)	1 (1.5)	1.000
Some other first operation, n (%)[f]	2 (2.6)	0 (0.0)	2 (3.1)	1.000
Had other surgery in first 24 hours, n (%)	29 (36.7)	6 (42.9)	23 (35.4)	0.761
Admitted to ICU/HDU, n (%)[a]	52 (66.7)	9 (69.2)	43 (66.2)	1.000
Tracheostomy, n (%)	4 (7.7)	0 (0.0)	4 (9.3)	1.000
Median duration of intubation, days	0 (0-3.5)	1.0 (0-4.5)	0 (0-4.0)	0.584
Median duration of ventilation, days	0 (0-3.8)	1.0 (0-5.0)	0 (0-4.0)	0.617
Median (IQR) duration of ICU/HDU stay, days	3.5 (2.0-7.8)	5.0 (3.5-17.5)	3.0 (2.0-7.0)	0.149

Abbreviation: ED = Emergency Department

[a] n=1 missing; [b] n=4 missing; [c] n=9 missing; [d] n=16 missing; [e] n=23 missing; [f] n=2 missing; [g] n=8 missing;

Appendix 2 – Supplementary Tables of Extracted Features for Machine Learning Analysis of rSO2 and HbI

	AUC all ≤ 45% segments > 1 min		No. of segments ≤ 45% lasting > 1 min		Sum of periods ≤ 45% (s)		Max length of ≤ 45% segments > 1 min		Minimum rSO_2 (%)		Mean rSO_2 (%)	
ID	*Ch 1*	*Ch 2*	*Ch 1*	*Ch 2*	*Ch 1*	*Ch 2*	*Ch1*	*Ch2*	*Ch1*	*Ch2*	*Ch1*	*Ch 2*
1	0	0	0	0	0	0	0	0	73.8	74	77	77.2
2	0	0	0	0	0	0	0	0	58.8	68.3	71.6	73.6
3	0	0	0	0	0	0	0	0	82.8	83.4	87.9	88.8
4	0	0	0	0	0	0	0	0	71.4	63.1	79.3	76.6
5	0	0	0	0	0	0	0	0	90	63	96.6	97.8
6	0	0	0	0	0	0	0	0	81.5	94	87.1	95.3
7	0	0	0	0	0	0	0	0	72.8	60.7	73.6	67.4
8	0	0	0	0	0	0	0	0	82.9	80.1	93.1	84.7
9	0	0	0	0	0	0	0	0	64	64.5	70.5	74
11	0	0	0	0	0	0	0	0	82.3	91	95.6	92.1
13	0	0	0	0	0	0	0	0	51.8	54.7	63.1	61.7
15	0	0	0	0	0	0	0	0	87.9	88.2	90.4	90.6
16	0	0	0	0	0	0	0	0	77.2	77.1	83.5	84.7
17	0	0	0	0	0	0	0	0	82.9	72.5	90.3	84.4
18	0	0	0	0	0	0	0	0	76	78.6	85.2	88
19	0	0	0	0	31	0	30	0	36.5	*NaN*	71.1	*NaN*
20	0	0	0	0	0	0	0	0	65.9	63.7	77.2	73.7
22	0	0	0	0	0	0	0	0	76.3	74.9	89.7	85.3
23	0	0	0	0	0	0	0	0	71.7	71	74.9	74
24	0	0	0	0	0	0	0	0	69.5	69.9	72.9	72.6
25	0	0	0	0	0	0	0	0	95	98	97.9	99.5
26	0	0	0	0	0	0	0	0	60.4	79.9	67.8	85.1
27	0	0	0	0	0	0	0	0	73.3	71	81.4	84.7
28	0	0	0	0	0	0	0	0	66	66.1	68.9	69.6
29	0	0	0	0	0	0	0	0	62.8	59.8	69.4	70.2
30	0	0	0	0	0	0	0	0	70	65	75	79.1
31	0	0	0	0	0	0	0	0	65	62	67.2	65
33	0	0	0	0	0	0	0	0	74.7	75	81.7	81.3
34	0	0	0	0	0	0	0	0	65.7	67.2	82.7	83.5
35	0	0	0	0	0	0	0	0	62.5	46.7	73.2	71
36	0	0	0	0	0	0	0	0	77.3	66	93.3	90.4
37	0	0	0	0	0	0	0	0	79.1	90.8	89.8	95.1
38	0	0	0	0	0	0	0	0	70.7	70.5	77.1	76.1
39	0	0	0	0	0	0	0	0	56.3	60.8	68.8	69.1
40	0	0	0	0	0	0	0	0	72	69.4	84.7	84.2
41	0	0	0	0	32	37	13	13	5	12	56.7	80.3
42	0	0	0	0	0	32	0	13	65.1	44.8	78.4	83.6
43	0	0	0	0	0	0	0	0	59.7	55.1	77.8	75.5
44	0	0	0	0	0	0	0	0	57.4	55.3	70.2	62.6

45	0	0	0	0	0	0	0	0	70	73.9	74.5	75.9
46	0	0	0	0	0	0	0	0	73	69.8	74.6	72.8
47	0	0	0	0	0	0	0	0	59.1	62.3	71.1	71.7
48	0	0	0	0	0	0	0	0	71.6	71.3	79.2	76.5
49	0	0	0	0	0	0	0	0	65.3	72.4	69.9	76.4
50	0	0	0	0	21	0	21	0	17.3	54.8	68.5	67.9
51	0	0	0	0	0	0	0	0	71.8	74.6	80.4	78.8
52	0	0	0	0	1	0	0	0	45	68.2	83.4	78.5
53	0	0	0	0	0	0	0	0	70.4	76.9	89.9	91.8
54	0	0	0	0	0	0	0	0	67.9	68	72.3	72.5
55	2034.1	0	1	0	151	0	108	0	1.9	64.1	49.2	73.5
56	0	0	0	0	0	0	0	0	45.9	57.5	68.4	63.8
57	0	0	0	0	0	0	0	0	99	87	100	92.2
58	0	0	0	0	0	0	0	0	59.8	63	66.4	68.8
59	0	0	0	0	0	0	0	0	64.4	67.8	79.8	83.6
60	0	0	0	0	0	0	0	0	76	70.3	81.6	75.2
61	0	0	0	0	0	0	0	0	68.3	71.5	70.9	73.5
62	0	0	0	0	0	0	0	0	63.6	75.8	78.6	88.5
63	8666.4	0	2	0	731	0	492	0	17.7	73.1	33.8	83.1
64	0	0	0	0	0	0	0	0	76.4	79	79.4	80.8
65	0	0	0	0	0	0	0	0	66.6	70.8	69.7	82.1
66	0	0	0	0	0	0	0	0	78.1	77.2	84.8	85.7
67	0	0	0	0	0	0	0	0	66.5	65.8	73.1	74.7
68	0	0	0	0	0	0	0	0	76.6	65.8	80.9	79.2
69	0	0	0	0	0	0	0	0	74	72.5	82.3	76.6
70	0	0	0	0	0	0	0	0	*NaN*	67.5	*NaN*	78.1
71	0	0	0	0	0	0	0	0	*NaN*	69.9	*NaN*	85.1
72	0	0	0	0	0	0	0	0	*NaN*	78.3	*NaN*	84.6
73	0	0	0	0	0	0	0	0	*NaN*	56.1	*NaN*	58.6
75	0	0	0	0	0	0	0	0	79.5	80.7	85.5	87.2
76	0	0	0	0	100	0	49	0	3.1	57.2	61.2	83.9
77	0	0	0	0	0	0	0	0	75.9	64.1	77.9	69.1
78	0	0	0	0	0	0	0	0	77.7	72.1	84.1	84.3
79	0	0	0	0	0	0	0	0	74.5	76.3	81.2	84.3
80	0	0	0	0	0	0	0	0	59.5	74.2	67.6	78.6
81	0	0	0	0	0	0	0	0	62.8	68.1	83.5	79.1
82	0	0	0	0	0	0	0	0	66.6	71.3	81.3	83.7
84	0	0	0	0	0	0	0	0	73.4	74.5	82.2	84.3
85	0	0	0	0	0	0	0	0	61.5	62.2	64.3	66
86	0	0	0	0	0	0	0	0	55	64.1	71.5	76.5
87	0	0	0	0	0	0	0	0	79	84.9	82.7	88.3
88	0	0	0	0	0	0	0	0	48.2	67.3	78.3	78.9

Supplementary Content for Machine Learning Analysis Table 2: Extracted Features for rSO_2

	AUC all ≤ 1 g/dL segments > 1 min		No. of segments ≤ 1 g/dL lasting > 1 min		Sum of periods ≤ 1 g/dL (s)		Max length of ≤ 1 g/dL segments > 1 min		Minimum HbI (g/dL)		Mean HbI (g/dL)	
ID	*Ch 1*	*Ch 2*	*Ch 1*	*Ch 2*	*Ch 1*	*Ch 2*	*Ch1*	*Ch2*	*Ch1*	*Ch2*	*Ch1*	*Ch 2*
1	37	0	1	0	223	0	223	0	1.1	1.3	1.2	1.4
2	44.1	76.3	2	2	391	566	207	290	1	1	1.3	1.1
3	664	664	1	1	664	664	664	664	0	0	0	0
4	59.8	32.5	2	1	361	301	289	272	0.3	1	1.3	1.4
5	46.2	0	1	0	101	33	84	33	0	0	0.5	0.4
6	822	822	1	1	822	822	822	822	0	0	0	0
7	0	0	0	0	0	0	0	0	1.4	1.2	1.4	1.2
8	154.7	51.6	1	1	314	413	314	413	0.2	1	0.5	1.1
9	73.7	83.7	1	1	891	895	891	895	0.9	0.8	0.9	0.9
11	0	0	0	0	84	0	48	0	0.2	1.4	1.2	1.4
13	64.1	95.8	1	1	599	599	599	599	1	1.2	1.1	1.2
15	661	662	1	1	661	662	661	662	0	0	0	0
16	966	970	1	1	966	970	966	970	0	0	0	0
17	0	0	0	0	58	0	58	0	-1.5	1.2	1.4	1.3
18	74.1	35.6	2	2	531	359	286	148	1	0.5	1.2	1.2
19	0	0	0	0	137	0	59	0	0.5	*NaN*	1.2	*NaN*
20	18.5	17.8	1	1	89	471	61	435	0	1	1.3	1.2
22	0	0	0	0	0	0	0	0	1.3	1.5	1.5	1.6
23	16.6	0	1	0	131	18	87	13	1.2	1.2	1.2	1.2
24	108.5	0	1	0	665	0	665	0	1.1	1.3	1.2	1.3
25	7.8	60.9	1	2	521	516	521	357	1	1.1	1	1.1
26	0	24.9	0	1	0	157	0	134	1.3	1.2	1.4	1.2
27	0	0	0	0	0	23	0	16	1.2	1	1.3	1.2
28	0	0	0	0	0	0	0	0	1.3	1.2	1.3	1.3
29	14.7	34.9	1	1	447	447	447	447	0.9	1	1	1.1
30	216.2	0	1	0	341	5	341	5	0.3	0.4	0.4	1
31	146.9	101.4	2	1	846	856	501	856	1.1	1.1	1.2	1.1
33	0	36.3	0	1	0	210	0	210	1.3	1.1	1.3	1.9
34	153.2	35.5	1	1	902	292	902	259	1.1	1.1	1.2	1.2
35	14.8	110.3	2	1	142	596	81	522	0.9	0.3	1.3	1
36	332.9	225.7	1	1	770	599	766	464	0.5	0.2	0.7	0.7
37	108.4	364.1	1	1	346	714	346	714	0.1	0.4	0.7	0.5
38	136.3	0	1	0	689	0	689	0	0.6	1.4	0.8	1.4
39	104	113	3	2	858	773	454	464	1	1.1	1.1	1.2
40	186.9	0	1	0	445	28	401	28	-0.2	0	0.9	1.4
41	0	0	0	0	58	37	45	30	0	0	0.7	0.9
42	73.2	290.9	1	1	205	805	205	805	0.6	0.4	0.6	0.6
43	60.6	38.2	2	2	386	437	209	224	0.3	1	1.2	1.2
44	0	29.6	0	1	219	79	31	79	1.2	-0.4	1.2	1.2
45	0	0	0	0	0	0	0	0	1.3	1.4	1.3	1.4
46	35.1	39	1	1	246	266	204	266	1.2	1.1	1.2	1.1
47	74.8	97.6	1	1	884	884	884	884	1	1	1.1	1.1
48	0	106	0	1	0	680	0	680	1.3	1.1	1.3	1.2

49	110.9	110.2	1	1	842	842	842	842	0.7	0.9	1.1	1.1
50	28.6	0	1	0	106	57	82	38	-0.2	-0.1	1.2	1.3
51	0	0	0	0	0	304	0	17	1.3	1.2	1.3	1.2
52	34.6	42.2	1	1	335	345	335	345	0.8	0.4	1.1	0.9
53	51.6	30.2	2	1	195	337	104	337	0.1	0	0.9	1
54	0	0	0	0	0	0	0	0	1.2	1.3	1.3	1.4
55	181.5	0	1	0	318	0	318	0	0.2	1.2	0.6	1.3
56	19.6	60.1	2	1	307	798	116	798	0.9	0.8	1.2	0.9
57	0	0	0	0	56	5	26	5	1.5	0.9	0.9	1.4
58	177	15.7	1	1	1010	196	1010	85	1.2	1.2	1.2	1.2
59	93.5	453	1	2	158	881	158	808	0.2	0.4	0.4	0.5
60	0	0	0	0	19	6	19	3	0.4	1.2	1.2	1.3
61	0	32.2	0	1	124	308	20	176	1.2	1.2	1.2	1.2
62	43.6	0	1	0	430	6	327	3	0	1.2	1.1	1.3
63	66.5	0	1	0	767	0	767	0	0.8	1.4	0.9	1.6
64	85.8	171.1	1	1	1043	1049	1043	1049	1	1.1	1.1	1.2
65	0	0	0	0	154	35	51	35	1.2	0.1	1.2	1.4
66	73.6	62.2	1	1	628	709	628	709	1	1	1.1	1.1
67	111.6	0	1	0	677	0	655	0	1.1	1.2	1.2	1.4
68	75.4	57	1	1	544	548	544	548	1	0.5	1.1	1.1
69	14	202.3	1	2	205	436	89	279	1.1	0.1	1.2	0.8
70	0	217.7	0	4	0	563	0	216	*NaN*	-1.1	*NaN*	1
71	0	124.9	0	1	0	309	0	301	*NaN*	0.5	*NaN*	1.1
72	0	69.2	0	1	0	551	0	551	*NaN*	0.8	*NaN*	1.1
73	0	0	0	0	0	0	0	0	*NaN*	1.4	*NaN*	1.5
75	301.4	84.8	1	1	568	311	568	311	0.5	0.6	0.5	0.7
76	119.5	72.2	2	2	449	276	339	123	0	0.2	1	1.1
77	0	20.1	0	1	24	469	17	469	1.1	0.9	1.2	1
78	0	23	0	1	0	110	0	110	1.3	0.6	1.4	1.3
79	148.9	123.8	1	1	1024	971	1024	971	1.1	1.1	1.1	1.1
80	36.5	20.2	1	1	577	547	577	547	0.8	0.9	0.9	1
81	138.2	51.4	1	3	868	424	868	150	1	1.1	1.2	1.2
82	0	0	0	0	0	0	0	0	1.3	1.5	1.5	1.7
84	102.6	60.9	1	1	942	187	942	139	0.2	-0.2	1	1.2
85	18.7	47.9	1	1	672	905	672	905	0.9	0.2	1	1
86	53.9	0	1	0	1249	0	1249	0	1	1.3	1	1.3
87	127.5	43.4	1	1	1131	362	1131	225	1.1	1.2	1.1	1.2
88	0	0	0	0	224	31	57	13	0.8	0.2	1.2	1.5

Supplementary Content for Machine Learning Table 3: Extracted Features for HbI