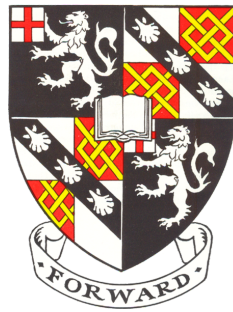# Intracranial Monitoring after Severe Traumatic Brain Injury

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This dissertation is submitted for the degree of

Doctor of Philosophy

Supervised by Marek Czosnyka and Peter Smielewski

Churchill College

University of Cambridge

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Preface

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text.

It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text.

It does not exceed the prescribed word limit for the relevant Degree Committee (60000 words).

Joseph Donnelly,
September 2017

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To colleagues from Aoteroa including Daniel, James, and Katie; thank you for your friendship and laughs. Thank you James for your invaluable assistance with programming and statistical queries.

Professors Hutchinson and Menon, I thank you both for scientific and administrative support as department heads.

Without financial support from the Woolf Fisher trust, this project would not have been possible. In particular, I would like to acknowledge Nigel and Jan Evans for providing personal support and a reminder of home during annual visits.

Finally, I am indebted to the patients who participated in the studies of this thesis.

Abbreviations

- **aABP** amplitude of ABP
- **ABP** arterial blood pressure
- **AMP** pulse amplitude of ICP
- **BTF** brain trauma foundation
- **COx** cerebral oximetry index
- **CPP** cerebral perfusion pressure
- **CPPopt** optimal CPP
- **CSF** cerebrospinal fluid
- **CT** computed tomography
- **CVR** cerebrovascular resistance
- **ΔCPPopt** CPP minus CPPopt
- **EVD** external ventricular drain
- **FV** blood flow velocity
- **GCS** Glasgow coma scale
- **GOS** Glasgow outcome scale
- **O_2Hb** oxygenated haemoglobin
- **HHb** deoxygenated haemoglobin
- **HVx** haemoglobin volume reactivity index
- **ICP** intracranial pressure
- **IQR** interquartile range
- **LDF** laser Doppler flowmetry
- **LLA** lower limit of autoregulation
- **LLR** lower limit of reactivity
- **MRI** magnetic resonance imaging
- **Mx** mean flow index
- **NCCU** neurocritical care unit
- **NIRS** near-infrared spectroscopy
- **OR** odds ratio
- **ORx** oxygen reactivity index
- **$P_{BT}O_2$** brain tissue partial oxygen pressure
- **PET** positron emission tomography
- **RAP** cerebrospinal compensatory reserve
- **ROC** receiver operating characteristic
- **PAx** pressure amplitude index

- **PRx** pressure reactivity index
- **SAH** subarachnoid haemorrhage
- **TBI** traumatic brain injury
- **TCD** transcranial Doppler
- **THI** tissue haemoglobin index
- **TOI** tissue oxygenation index
- **TOx** total oxygenation reactivity index
- **ULA** upper limit of autoregulation
- **ULR** upper limit of reactivity
- **WLR** within limits of reactivity

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Summary

Intracranial monitoring after severe traumatic brain injury offers the possibility for early detection and amelioration of physiological insults. In this thesis, I explore cerebral insults due raised intracranial pressure, decreased cerebral perfusion pressure and impaired cerebral pressure reactivity after traumatic brain injury.

In chapter 2, the importance of intracranial pressure, cerebral perfusion pressure and pressure reactivity in regulating the cerebral circulation is elucidated along with a summary of the existing evidence supporting intracranial monitoring in traumatic brain injury. In chapter 4, intracranial pressure, cerebral perfusion pressure, and pressure reactivity insults are demonstrated to be common, prognostically important, and responsive to long-term changes in management policies. Further, while these insults often occur independently, coexisting insults portend worse prognosis. In chapter 5, I examine possible imaging antecedents of raised intracranial pressure and demonstrate that initial subarachnoid haemorrhage is associated with the subsequent development of elevated intracranial pressure. In addition, elevated glucose during the intensive care stay is associated with worse pressure reactivity. Cortical blood flow and brain tissue oxygenation are demonstrated to be sensitive to increases in intracranial pressure in chapter 6. In chapter 7, a method is proposed to estimate the cerebral perfusion pressure limits of reactivity in real-time, which may allow for more nuanced intensive care treatment. Finally, I explore a recently developed visualisation technique for intracranial physiological insults and apply it to the cerebral perfusion pressure limits of reactivity.

Taken together, this thesis outlines the scope, risk factors and consequences of intracranial insults after severe traumatic brain injury. Novel signal processing applications are presented that may serve to facilitate a physiological, personalised and precision approach to patient therapy.

Chapter 1

Introduction and working hypotheses

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality worldwide and its burden on society is increasing. Decreasing this burden will depend in part on improving our understanding of TBI pathophysiology. After the primary injury, a myriad of pathophysiological pathways are set into motion, that if left unchecked, result in permanent disability or death. Effective monitoring of these pathways is key to the acute management of severe TBI on the premise that early detection and correction of abnormal physiology may lead to improved outcomes. Because maintaining the delivery of oxygen and nutrients to the brain via cerebral blood flow (CBF) is essential for a functioning brain, intracranial haemodynamics form a core component of neuromonitoring after severe TBI.

Because CBF is proportional to the pressure gradient across the cerebral vascular bed, monitoring after severe TBI often includes monitoring of the difference between the upstream arterial pressure (ABP) and effective downstream pressure – the intracranial pressure (ICP). The difference between ABP and ICP is denoted the cerebral perfusion pressure and is used clinically to help guide treatment along with the ICP value *per se*. Pertinent to TBI is the ability of the cerebral blood vessels to react to changes in CPP. This process–termed cerebral autoregulation (CA)–is impaired after TBI and can be estimated by the relationship between slow changes in ABP and ICP. In this thesis, I explore several advanced aspects of intracranial monitoring of ICP, CPP and PRx after TBI.

The four major aims of this thesis provide the basis for each of the result chapters (4,5,6,7):

1. Describe the prevalence, relevance, and secular trends of disturbed ICP, CPP and PRx after severe TBI.

2. Identify clinical associations of deranged PRx and ICP.

3. Examine physiological consequences of severe increases in ICP.

4. Use CPP and PRx signals to continuously estimate the CPP limits of reactivity.

In the following chapters, I review contemporary literature (chapter 2), outline methods used in this thesis (chapter 4.1.2) and then detail each of the 8 studies relating to the

above hypotheses. In the final chapter a summary of the main results and future research directions are explored.

1.1 Descriptive analyses of ICP, CPP, and cerebral autoregulation monitoring after TBI

While the continuous assessment of ICP, CPP and cerebral autoregulation has been available for over 20 years, the proportion of patients that experience sustained derangement in these variables is unknown. Furthermore, the management of TBI patients at our institution has evolved over the quarter century, but how this has affected intracranial monitoring variables has not been described.

1.1.1 Hypotheses

- Episodes of disturbed PRx will mainly occur with disturbed ICP or CPP.

- The prevalence of elevated ICP and low CPP will have decreased owing to changes in TBI management over the past 25 years.

1.2 Clinical associations of CPP, ICP and cerebral autoregulation after TBI

After the initial trauma, a plethora of systemic and local processes are activated which may contribute to patient prognosis. Whether these processes influence monitored intracranial physiology is unclear. Markers from the initial injury may be apparent on the initial CT scan such as petechial haemorrhages or traumatic subarachnoid haemorrhage, as may indicators of evolving pathology such as mid-line shift or compressed basal cisterns. Alterations in arterial blood glucose may also occur as a consequence of trauma and have the potential to affect vascular function.

1.2.1 Hypotheses

- Pathology on initial brain CT scan will influence subsequent ICP on the intensive care unit.

- Increased arterial glucose will be related to disturbed PRx.

1.3 Intracranial sequelae of raised ICP

Raised ICP if unchecked can lead to transtentorial herniation and brain death, underscoring the potential benefit of clinical monitoring. However, how raised ICP effects cerebral

haemodynamics is unclear. In this chapter, two complementary approaches are used:

1. Experimental increases in ICP with artificial cerebral spinal fluid infusion in NZ rabbits;

2. Observations from TBI patients developing severe refractory intracranial hypertension.

1.3.1 Hypotheses

- During experimental increases in ICP, decreased cerebral vasomotor tone and increased arterial blood pressure will protect cerebral perfusion.

- After TBI, severe increase in ICP will cause progressive deterioration in PRx and decrease in brain oxygenation ($P_{BT}O_2$).

1.4 Novel applications of intracranial monitoring after TBI

Cerebral autoregulation assessment using PRx has been used to define a continuous estimation of 'optimal' CPP. Extending this approach to define the CPP lower limits of reactivity (LLR) and upper limits of reactivity (ULR) has not been studied in TBI and may provide clinically useful information.

1.4.1 Hypotheses

- A CPP outside the PRx defined individualised CPP limits of reactivity will associate with patient outcome after TBI.

- ICP insults with a CPP below the lower limit of reactivity will be more harmful than with CPP above the lower limit of reactivity.

Chapter 2

Physiology and literature review; intracranial monitoring after severe traumatic brain injury

The following publications formed the basis of this chapter:

- Donnelly, J., Budohoski, K.P., Smielewski, P. and Czosnyka, M., 2016. Regulation of the cerebral circulation: bedside assessment and clinical implications. Critical care, 20(1), p.129.

- Donnelly, J., Aries, M.J. and Czosnyka, M., 2015. Further understanding of cerebral autoregulation at the bedside: possible implications for future therapy. Expert review of neurotherapeutics, 15(2), pp.169-185.

- Donnelly, J. and Czosnyka, M., 2014. The thermodynamic brain. Critical care, 18(6), p.693.

The regulation of cerebral blood flow (CBF) relies on the complex interplay between cardiovascular, respiratory, and neural physiology. In health, these physiologic systems act to maintain an adequate CBF through modulation of hydrodynamic parameters; the resistance of cerebral vessels, as well as the arterial, intracranial, and venous pressures. After TBI, however, one or more of these parameters can be compromised raising the possibility of disturbed CBF regulation and its pathophysiologic sequelae.

The rigorous assessment of the cerebral circulation requires not only measuring CBF and its hydrodynamic determinants, but also assessing the stability of CBF in response to changes in arterial pressure (cerebral autoregulation) and the reactivity of CBF to a vasodilator (CO_2 reactivity). Ideally, cerebral circulation monitors should be continuous, physically robust, allow for both regional and global CBF assessment, and be conducive to application at the bedside.

2.1   Regulation of the cerebral circulation

To function, the brain requires an adequate delivery of nutrients and oxygen. Therefore, a circulatory system is required to maintain an optimal CBF for the brain's diverse needs. Whilst oxygen and nutrient delivery is in part dependent on the pump supplying it–the heart–the brain has also evolved mechanisms to ensure the precise control of its perfusion; the cerebral vessels have the remarkable ability to rapidly adapt and react to the brain's chemical environment, to neuronal signals, and to the pressure within the cerebral vessels.

A haemodynamic model for the cerebral circulation has been described that aids understanding of how CBF is regulated[1,2]. In such a model, CBF is dependent on the pressure supplied in the cerebral arteries (the arterial blood pressure- ABP), the back pressure in the cerebral venous system (usually close to intracranial pressure-ICP), and the resistance related to the diameter of the small cerebral vessels (cerebrovascular resistance-CVR; figure 2.1. Thus, cardiovascular, intracranial pressure, and cerebrovascular components are all important regulators of the cerebral circulation. Applying this model can provide crucial insights into the physiologic factors that regulate cerebral perfusion in health and elucidate why CBF regulation is often impaired in pathologic states.
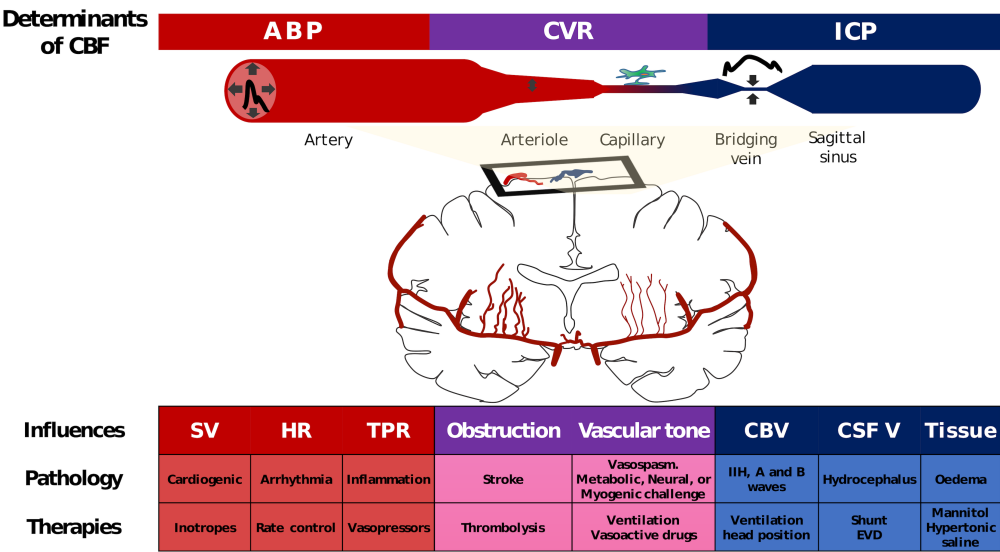
Figure 2.1: **Regulation of the cerebral circulation.** CBF is directly proportional to the cerebral perfusion pressure (difference between ABP and ICP) and inversely proportional to cerebrovascular resistance. Intracranial pressure exerts its effect on CBF by compression of the venous vasculature where the bridging veins enter the sagittal sinus, ensuring that bridging vein and post-capillary intravascular pressure is always above ICP. CBF is modulated by the cardiovascular system in terms of the regulation of SV, HR, and TPR (in red). Control of TPR with vasopressors forms an integral part of many CBF protective strategies (even when TPR is not the primary cause of CBF disturbance). CVR is regulated at the level of the arterioles (in purple) by variations in vascular tone in response to metabolic, neural or myogenic inputs. ICP (in blue) modulates CBF through its coupling with cerebral venous pressure. ICP increases can be caused by increases in cerebral blood, CSF, or parenchymal volume. All therapies that modulate CBF do so via one (or more) of these pathways. There is typically significant interdependence between the therapies, determinants and influences of CBF. *ABP* arterial blood pressure; *CBF* cerebral blood flow; *CBV* cerebral blood volume; *CSF V* cerebrospinal fluid volume; *CVR* cerebrovascular resistance; *HR* heart rate; *ICP* intracranial pressure; *SV* stroke volume; *TPR* total peripheral resistance.

2.1.1 The cardiovascular component

As early as 1890, Sherrington and Roy underlined the importance of the ABP in the regulation of CBF:

> "One of the most evident of the facts observed by us is that the blood-supply of the brain varies directly with the blood pressure in the systemic arteries"

—Roy and Sherrington, 1890.

The pressure that supplies the cerebral vessels is dependent on factors mostly outside of the brain itself: the heart provides the cardiac output while the peripheral vessels provide the resistance, both of which contribute to the ABP supplying the brain. In this sense, the balance between the brain cerebrovascular resistance and the total peripheral resistance determines the proportion of the cardiac output that reaches the brain. Thus, any pathological or physiological event that affects the heart or the vasculature as a whole has the potential to alter the cerebral circulation. Thus, conditions such as cardiogenic shock and arrhythmia (conditions that that may co-exist or develop in the setting of severe TBI) impair CBF[3], as do conditions that effect the systemic vasculature such as sepsis[4].

Just as pathologies affecting ABP can influence CBF, therapies to augment CBF often do so by modulating ABP[5,6]. Vasopressors act to buffer ABP by constricting peripheral vessels, while inotropes and cardiopulmonary bypass machines act to modulate cardiac output (figure 2.1). An important consideration of such ABP augmentation based approaches is that the relationship between changes in ABP and CBF is typically non-linear due to active changes in vascular tone occurring at the level of the cerebral arterioles—due to cerebral autoregulation[7–10]. Furthermore, modulating ABP as a therapeutic measure will not only increase blood flow to the brain, it will also increase blood flow to any vascular beds with a low vascular resistance.

2.1.2 The intracranial pressure component

At the distal end of the microvasculature is the cerebral venous pressure. This provides a back pressure that impedes CBF. The venous pressure in turn is related to both the venous pressure in the larger cerebral veins and the intracranial pressure. If the ICP is above the pressure in the lateral lacunae that feed into the large venous sinuses (that are exposed to the CSF space, figure 2.1), then these vessels will be compressed leading to a post-capillary venous pressure just above ICP[11,12]. Thus, any increase in ICP has the potential to decrease the longitudinal pressure gradient across the vascular bed – the cerebral perfusion pressure (CPP=ABP-ICP) – and, provided there are no compensatory changes in CVR, decrease CBF.

Because the skull is rigid, any increase in volume of a brain compartment can cause an increase in ICP[13]. Increases in volume of the intravascular compartment, the CSF compartment or the brain parenchymal compartment can all increase ICP and therefore have the potential to decrease CBF. These compartmental volume changes could be caused by vascular dilation, hydrocephalus or cerebral oedema. Therapies that alter CBF via ICP changes include mild hyperventilation to decrease vascular volume (although the relationship between CO_2 and CBF is complex), CSF diversion through external ventricular drainage to decrease CSF volume, osmotherapy to reduce the brain tissue volume or decompressive craniectomy to increase the space available for the brain parenchyma (figure 2.1)[14].

2.1.3 The cerebrovascular component

At the level of the brain vessels themselves, CBF can be controlled by active changes in the diameter of the 'regulating' vessels, thus influencing the cerebral vascular resistance (CVR). The major site of active regulation of the cerebral circulation is thought to occur at the level of the arterioles with their thick smooth muscle layer and ability for profound dilation and constriction[1,2]. However, larger conduit arteries, capillaries, and venous structures may also be important in certain situations[15–18]. For example, during neuronal activation, relaxation of pericytes surrounding capillaries has been considered to account for a large proportion of the flow increase[16]. Cerebral venules and veins are characterized by a low density of smooth muscle cells and therefore have the ability to increase volume with any increase in pressure; i.e., they exhibit a high compliance[18]. While probably not important in the active regulation of CBF, the compliant nature of venous structures may play a passive role in the regulation of CBF; for example, arteriolar dilation leads to an increase in volume of post capillary venules that increases cerebral blood volume[19] and by extension could increase ICP, decrease CPP and therefore limit the increase in CBF.

In health, such changes in cerebral vascular resistance or CBF are most obvious during brain activation; an increase in neuronal activity elicits a prompt and significant increase in CBF[20] mediated through vessel dilation. Alternatively, during an ischaemic stroke, a portion of the cerebral vasculature is mechanically occluded by a thrombus causing a localised increase in CVR and decrease in CBF. During the vasospasm associated with subarachnoid haemorrhage, large cerebral arteries constrict, again resulting in an increased local CVR, and decreased CBF[21].

Changes in vascular tone of the cerebral vessels are caused by putative constricting and dilating substances. Such vasoactive substances may be supplied to the vessels via the blood stream (e.g. arterial pCO_2), produced locally (see neurovascular coupling below), or reach the smooth muscle fibres through direct autonomic innervation. Not surprisingly, this heterogeneity in the possible sites of vasoactive substance production can lead to difficulty in disentangling physiological mechanisms. For example, modulation of ventilation is commonly used to assess the function of the cerebral vasculature (see CO_2 reactivity below), however such a stimulus can in principle alter cerebrovascular tone through three separate mechanisms: changes in arterial PCO_2 reaching the brain[22], changes in autonomic activity[23], or direct changes in neuronal activity[24].

Synaptic transmission with its resulting glutamate release is the important stimulus for neurovascular coupling through the production of vasoactive metabolites such as arachidonic acid derivatives (20-hydroxy-eicosatetraenoic acid, prostaglandins, epoxyeicosatrienoic acids), lactate, adenosine and nitric oxide (NO)[15]. The site of production of these metabolites includes the neuron, the astrocyte and the smooth muscle cells themselves. Both neurons and astrocytes are ideally placed to mediate neurovascular coupling as they lie in close proximity to both the neuronal synapse where the signal is initiated and the smooth muscle cells of the regulating microvasculature; however, the relative importance

of neurons versus astrocytes for neurovascular coupling is uncertain[15]. Regardless of the site of production, the site of action is the smooth muscle fibres surrounding the arterioles or capillaries where the vasoactive substances produce changes in intracellular calcium concentration, smooth muscle contraction and vessel constriction. For further review on neurovascular coupling see[15,25–29].

The autonomic nervous system may also influence the vascular tone of cerebral vessels. Despite animal studies demonstrating a rich innervation of both the dilating parasympathetic and constricting sympathetic fibres, the autonomic control of CBF in humans remains controversial[30,31] with the divergence in opinions probably owing to between species variation in autonomic innervation, variations in brain metabolism between experiments and heterogeneous autonomic nerve distribution in the different studies[32]. Nevertheless, stimulation of the trigeminal ganglion in humans decreases estimated CBF[33] while blockade of the stellate ganglion increases estimated CBF[34], highlighting a role for the sympathetic nervous system in the regulation of the cerebral circulation in humans.

In addition to cerebrovascular resistance, mean arterial pressure and intracranial pressure, cardiac output has recently been suggested to be an independent regulator of CBF[35]. Evidence for such a view comes from studies that have demonstrated a change in CBF after interventions that change cardiac output but have no effect on MAP[35,36]. Thus, an additional measure of CBF regulation could be assessing CBF as a fraction of the cardiac output. Although, continuous and accurate measures of cardiac output are less practical than ABP, such an approach may provide additional insight into regional blood flow regulation in health and disease.

According to the conventional model (figure 2.1), for an increase in cardiac output to produce an increase CBF without a change in ABP, both total peripheral resistance and cerebrovascular resistance must decrease. As such, the autonomic nervous system has been speculated as the mechanism by which changes in cardiac output may alter CBF without changes in ABP[35], however, a metrological issue should also be considered. The arterial blood pressure measured in the examined studies (and the majority of vascular regulation investigations) is not the arterial blood pressure in the large cerebral arteries, but the pressure in a small peripheral vessel, or estimated non-invasively at the finger or arm. Thus, in situations where an increase in cardiac output causes an increased CBF and seemingly unchanged ABP (estimated at the arm), it is possible that cerebral arterial pressure actually increases. This issue needs to be verified, likely in an animal model.

Finally, the simple schema provided in figure 2.1 must be interpreted with the knowledge of the interdependence of variables. The cerebral circulation appears to have several cerebroprotective mechanisms; for example, if ABP decreases, aortic and carotid baroreceptors will alter autonomic outflow to increase HR and therefore buffer ABP and CBF[37]. Similarly, as proposed by Lassen, in response to a decrease in ABP, vessels will dilate in attempt to buffer CBF[7]. These important cerebroprotective processes are known as baroreceptor sensitivity and cerebral autoregulation, the latter of which will be discussed

in detail because of its important role after TBI.

2.2 Methods of intracranial haemodynamic monitoring

Given the myriad of physiologic situations after TBI that could critically impair the cerebral circulation, the availability of accurate and practical intracranial haemodynamic assessment methodologies is crucial. Often the choice of an appropriate measurement technique is a pragmatic one that depends upon the clinical scenario; a balance between availability, accuracy and practicality must be reached.

Non-invasive monitoring techniques include transcranial Doppler (TCD) and near infrared spectroscopy (NIRS) (for recent review see[38,39]). Such modalities have several important advantages making them suitable for interrogating CBF regulation in the clinical setting (table 1). First, both TCD and NIRS systems are portable and non-invasive, making assessment feasible in the emergency room, the critical care unit, or the operating theatre. Moreover, they capture high frequency and continuous data that can be combined with other modalities (such as ABP, or end-tidal CO_2) to give information on cerebral autoregulation and CO_2 reactivity (see sections 2.2.3 and 2.2.2).

Invasive cerebral perfusion methods include brain tissue oxygen oximetry, laser Doppler flowmetry, and thermal diffusion (for review of methodology principles[40–42]). Whilst obviously only suitable for critically ill patients due their invasive nature, these methods have the advantage of being relatively robust for long-term monitoring of the cerebral circulation. Brain imaging techniques (CT, PET, and MRI based) have the advantage of offering a high spatial resolution of CBF data and the ability to assess absolute CBF but are at present not suitable for bedside monitoring due to size, temporal resolution and radiation exposure[43]. A summary of CBF measurement techniques is provided in table 2.1.

Table 2.1: Methods for assesing cerebral blood flow (continued below)

	Principle	Global or local CBF assessment	Robustness	Invasive
TCD	Doppler	Global	Fair	No
NIRS	Absorbance of O_2Hb and HHb	Local	Good	No
P$_{BT}$O$_2$	Clark electrode	Local	Excellent	Yes
LDF	Doppler	Local	Excellent	Yes
Thermal diffusion	Thermal diffusion	Local	Excellent	Yes
Duplex US	Doppler	Global	Poor	No
CT	Attenuation of Iodine contrast (perfusion CT) or Xe gas	Global and local	Excellent	Minimal
PET	Radioactive tracers emit positrons dependent on perfusion	Global and local	Excellent	Minimal (IV access)
MRI	Perfusion dependent T2 signal changes with gadolinium	Global and local	Excellent	Minimal (IV access or none for arterial spin labelling)

	Bedside	Continuous	Advantages	Disadvantages
TCD	Yes	Yes	High frequency signal	Signal easily lost. Flow velocity assessment only
NIRS	Yes	Yes	Easy application	Uncertain extracranial contribution to signal
P$_{BT}$O$_2$	Yes	Yes	Robust	Local
LDF	Yes	Yes	Assesment of microcirculation	Unknown biological zero

	Bedside	Continuous	Advantages	Disadvantages
Thermal diffusion	Yes	Yes	Absolute CBF	Frequent calibrations
Duplex US	Potentially	No	Absolute and global	Semi-continuous
CT	Potentially	No	Global and local	Bulky and intermittent
PET	No	No	Global and local	Radiation, requires a cyclotron
MRI	No	No	Absolute, regional and global CBF	Time consuming, expensive, difficult for critically ill patient

TCD – transcranial Doppler; NIRS- Near infrared spectroscopy; $P_{BT}O_2$-Pressure of brain tissue oxygen; LDF- laser Doppler flowmetry; US- ultrasound; CT-computerised tomography; PET- positron emission tomography, MRI-magnetic resonance imaging; HHb-Deoxygenated haemoglobin, O_2Hb-oxygenated haemoglobin.

Because of the interdependence of the factors controlling CBF, it is important to measure these factors (ABP and ICP) in addition to CBF. Further, one can assess the regulation of the system by assessing the efficiency of the cardiac maintenance of ABP through the baroreflex sensitivity, and the brain vascular reactivity using the CBF reactivity to a dilatory stimulus (CO_2 reactivity), to a perfusion pressure challenge (cerebral autoregulation) or to a burst of neuronal activity (neurovascular coupling). Such extended assessment allows for a comprehensive understanding of the vulnerability of a patients cerebral circulation. Below we review 5 key aspects of intracranial haemodynamic monitoring common after TBI; ICP monitoring, CPP monitoring, neurovascular coupling, CO_2 reactivity, and then an extended discussion about cerebral autoregulation assessment.

2.2.1 ICP and CPP monitoring

Intracranial pressure monitoring has become a standard of care after severe TBI, but is also used after some cases of subarachnoid haemorrhage (SAH) or large ischaemic strokes. Because the brain sits within the rigid cranium, increases in volume of any of the three major compartments (tissue, blood, CSF) cause increases in ICP. In this way, monitoring of ICP can warn the clinician of a dangerous physiological state such as evolving oedema, expanding contusions or the development of hydrocephalus. Whatever the cause, increases in ICP have the potential to decrease global perfusion through a decrease in CPP as

demonstrated in figure 2.1, or to cause a dramatic decrease in local perfusion in areas of herniation. In herniation syndromes, due to the presence of pressure gradients within the skull, portions of brain tissue are pushed against rigid structures such as the foramen magnum, the tentorium cerebelli, or falx cerebri. Resultant local compression leads to dramatic decreases in CBF.

The measurement of intracranial pressure requires access inside the cranium, typically achieved with a frontal burr hole. While the most common location for measuring intracranial pressure is from the parenchyma, pressure can be transduced from different locations within the brain such as the subdural, epidural, or intraventricular spaces[44]. Intraventricular transducing is particularly useful in some circumstances, because a fluid filled intraventricular catheter can allow both intracranial pressure measurement and also allow for drainage of CSF as a measure to decrease an elevated ICP. Intraventricular drains, however, require a fluid filled transducing line and therefore carry additional risks of infection.

Because ICP influences cerebral venous pressure, it is often monitored along with ABP to give CPP. Like monitoring of ICP, monitoring of CPP is recommended after severe traumatic brain injury. CPP gives the clinician some indication of whether the brain is likely to be hypo or hyper perfused and also allows for careful titration of the major method to modulate CBF clinically- vasopressor therapy[45].

2.2.2 CO$_2$ reactivity

The cerebral vasculature is exquisitely sensitive to changes in the partial pressure of carbon dioxide in the arterial blood (p$_a$CO$_2$); decreases in p$_a$CO$_2$ causes cerebral resistance vessels to constrict and increases in p$_a$CO$_2$ causes cerebral vessels to dilate[22]. These alterations in vascular tone are probably mediated by changes in extracellular hydrogen ion concentration resulting from diffusion of CO$_2$ from inside the vessels. Several lines of evidence indicate that having a higher cerebrovascular reactivity may be a non-invasive and practical marker of cerebrovascular health (see 'clinical applications section below).

The CO$_2$ reactivity of cerebral vessels can be conveniently assessed at the bedside by measuring the CBF response to a decrease in p$_a$CO$_2$ (produced by hyperventilation) or by an increase in p$_a$CO$_2$ (by hypoventilating or adding inspired CO$_2$- hypercapnia). Typically, CO$_2$ reactivity is measured as the change in CBF as a fraction of the change in p$_a$CO$_2$:

$$Cerebrovascular\ CO_2\ reactivity = \frac{\Delta CBF\ (\%)}{\Delta p_a CO_2 (mm\ Hg)} \tag{2.1}$$

An important consideration is that changes in p$_a$CO$_2$ may also affect ABP or ICP and therefore changes in p$_a$CO$_2$ may alter CPP in addition to modulating vascular tone. Thus, in the ideal monitoring scenario, one would monitor CBF (perhaps using TCD), ABP (using an invasive arterial line or a non-invasive photoplethysmography device), p$_a$CO$_2$ (or end-tidal CO$_2$ as a surrogate), and in some situations – ICP.

Figure 2.2 demonstrates a CO_2 reactivity test in a TBI patient. In this case, TCD based flow velocity (Fv) was measured during moderate hyperventilation aimed to make the patient mildly hypocapnic. Because CO_2 reactivity is usually calculated as %change Fv/ mm Hg change in p_aCO_2, an important consideration easily appreciated from figure 2.1 and the reactivity equation (2.1) is that during a CO_2 reactivity test, any CO_2 influence on ABP or ICP may confound interpretation.
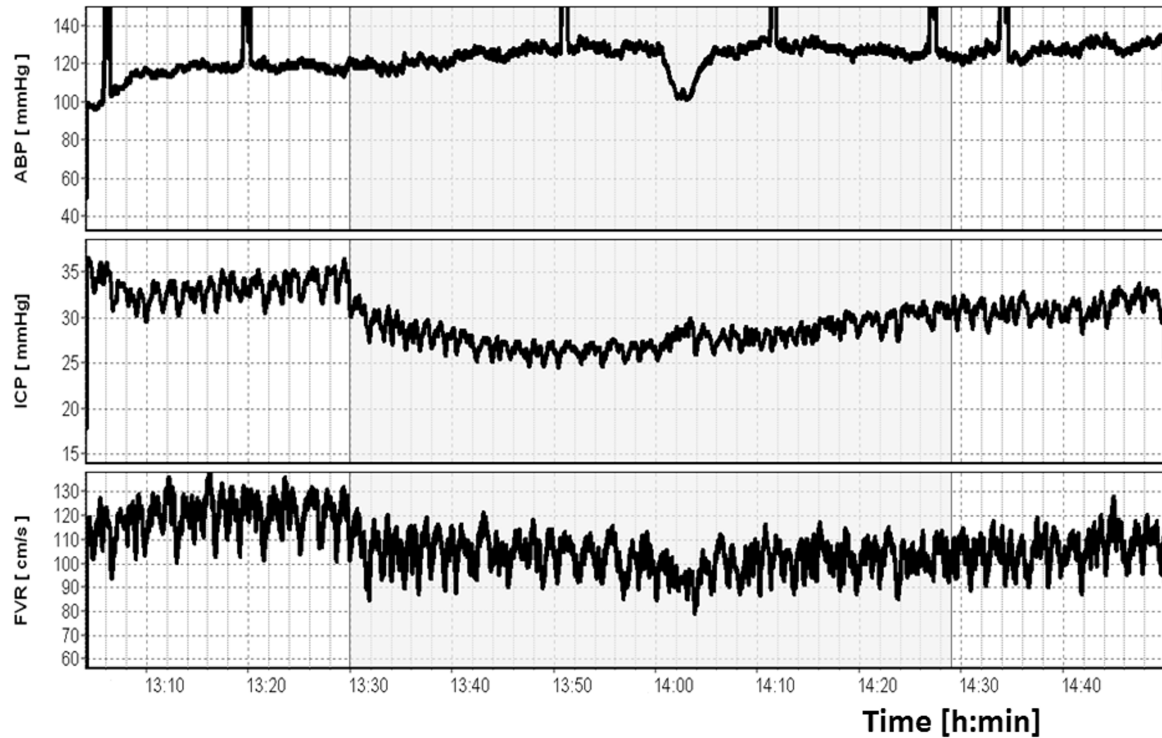
Figure 2.2: **Cerebrovascular CO_2 reactivity after TBI.** Carbon dioxide reactivity is a measure indicating how well vascular responses in the brain are preserved. Here mild active hyperventilation (p_aCO_2 challenge from 35 to 31.5 mm Hg) is applied temporarily (1 hour) in a patient after TBI. Right cerebral blood flow velocity (FVR) in middle cerebral artery decreased from 120 to 100 cm/s. CO_2 reactivity is calculated as p_aCO_2 this case reactivity is ~ 5 % / mm Hg - very good. However, at the same time ICP decreased from 32 to 27 mm Hg and blood pressure (ABP) increased from 120 to 125 mm Hg. Therefore, CPP increased from 88 to 98 mm Hg. The formula for CO_2 reactivity does not take into account the possible interaction between chemoregulation and autoregulation. Figure created from clinical monitoring data at Addenbrooke's hospital[46]. *ABP* arterial blood pressure; *ICP* intracranial pressure; *FVR* Flow velocity (right MCA).

2.2.3 Cerebral autoregulation

While cerebrovascular CO_2 reactivity gives information about the ability of the vessels to dilate or constrict in response to changes in p_aCO_2, cerebral autoregulation (CA) attempts to gain insight into vascular function from the response of cerebral vessels to changes in ABP (or in some cases – CPP). Unfortunately, the abundant and diverse methodologies

used to measure CA in the literature can render the concepts relevant to CA inaccessible to clinicians. The section that follows outlines some of the techniques and nomenclature that are commonly encountered in the CA literature.

Static vs. dynamic autoregulation measurements

Static autoregulation assessments refer to the relationship between changes in ABP and CBF at steady state—that is, the long-term CBF response to a sustained change in ABP. Conversely, dynamic assessments of autoregulation refer to changes in CBF in response to transient changes in ABP. Dynamic CA assessments require continuous measurements of ABP (e.g. from fluid filled pressure transducer attached to an indwelling arterial catheter, or from a non-invasive photoplethysmography device) and a surrogate of cerebral blood volume or CBF (e.g. transcranial Doppler (TCD), NIRS, brain oxygenation, ICP; see table 2.1). Dynamic CA is commonly tested with induced transient changes in ABP. Methods to change ABP for the purpose of dynamic CA assessment include deflation of supra-systolic thigh cuffs[47,48], postural manoeuvres[49], and lower body negative pressure[50].

Static cerebral autoregulation   The classic static assessment of autoregulation is the CA curve drawn by the Danish physiologist Niels Lassen. In his review, Lassen plotted steady state measurement pairs of ABP and CBF from 11 published studies, demonstrating an autoregulatory plateau and lower limit of autoregulation (LLA) for "man"[7]. From this review, it was widely concluded that the LLA for the human brain is at a mean ABP of 50 mm Hg. This hard doctrine persisted in medical practice until recent recognition that the LLA is highly variable across individuals and pathological conditions[51,52]. Regardless of the methods used to measure autoregulation (static or dynamic), some semblance of a static "Lassen's curve" has to be generated if the goal is to identify a LLA and assign ABP and CPP targets.

   In addition to delineating the lower limit of autoregulation from population data, steady state measurements of CBF and CPP can be assessed with a single, linear metric, the static rate of autoregulation. In this method, a single change in cerebral vascular resistance (CVR= CPP/CBF) is assessed in response to a single change in CPP[53]. If the assessments are done at perfusion pressures greater than LLA, then this metric is an assessment of the effectiveness of CA when supported by appropriate CPP. Typically, ABP is increased by the slow infusion of a vasopressor (such as phenylephrine) to slowly increase the ABP by ~20 mm Hg. In some individual cases, where ABP or CPP is highly variable, the full CA curve can be observed by plotting CBF averaged in groups of ABP or CPP (see figure 2.3).
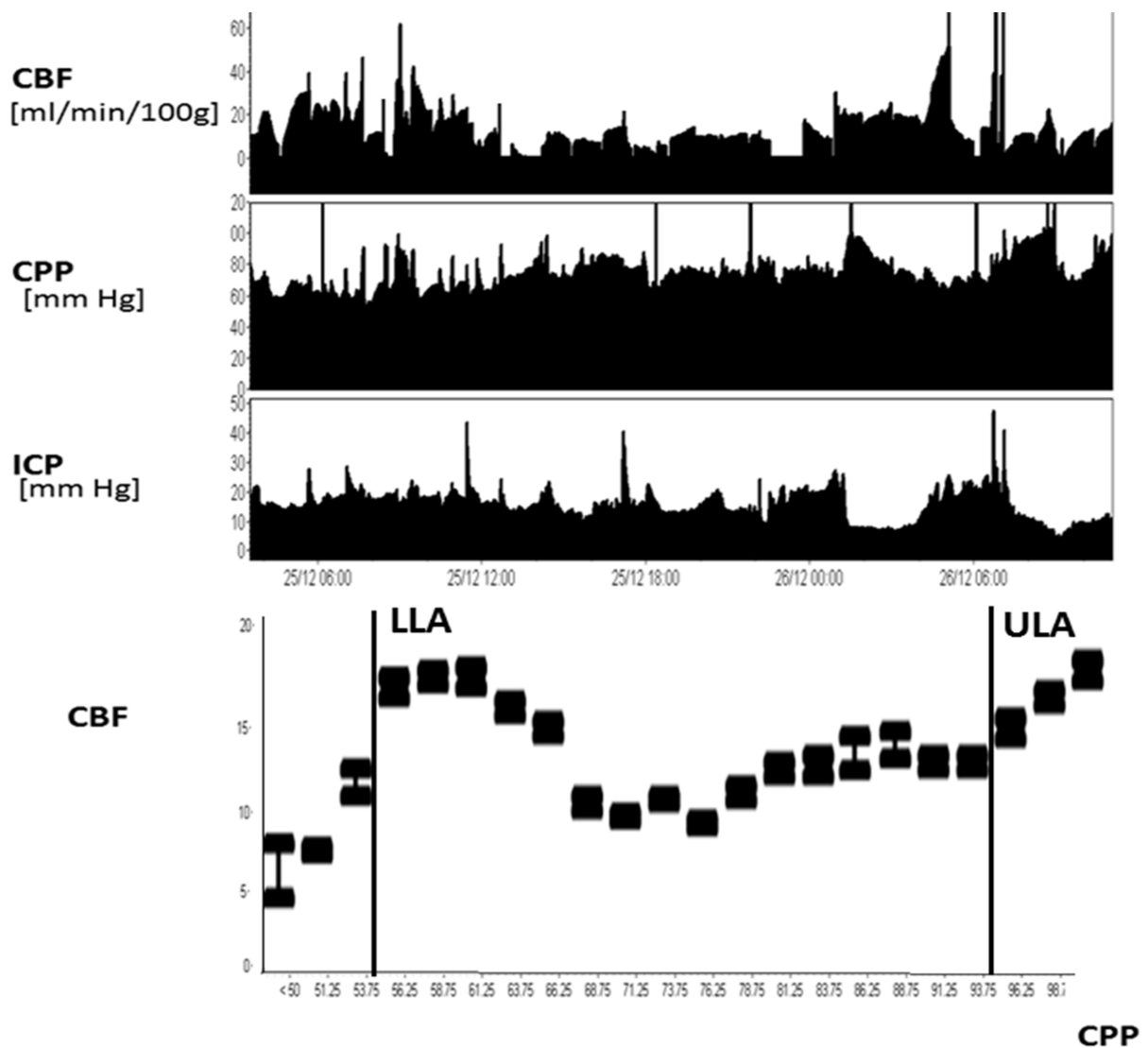
Figure 2.3: **Long term invasive CBF and CPP monitoring.** Example of the 'Lassen curve' depicting cerebral autoregulation. It is derived from long-term observation (48 hours) of thermal-dilution CBF and cerebral perfusion pressure (CPP) monitored in patient after severe brain injury. The curve shows lower (LLA) and upper (ULA) limits of autoregulation, outside which CBF is pressure-passive. Notably, within autoregulation range, CBF is not completely stable, but shows an increase in CBF around lower autoregulatory limit- which is commonly observed in patients under mild hyperventilation (in this case p_aCO_2 was on average 30 mm Hg). ICP- intracranial pressure. Figure created from clinical monitoring data at Sao Joao hospital, Portugal[46]. *CBF* cerebral blood flow; *CPP* cerebral perfusion pressure; *ICP* intracranial pressure; *LLA* lower limit of autoregulation; *ULA* upper limit of autoregulation.

Dynamic autoregulation An alternative approach to static autoregulation assessment is to continuously monitor the CBF response to natural slow variations ABP[54]. Such an approach has some important caveats: the natural ABP variations may not be strong enough to challenge CBF and changes in CBF could be caused by factors other than ABP. However, the advantages are that the monitoring poses no risk to the patients and since

the monitors can be applied continuously, one can assess long term trends in cerebral autoregulation within a patient. The analysis of slow spontaneous ABP fluctuations and CBF for CA assessment can grossly be divided into analyses in the time domain (using simple correlation methods) or in the frequency domain (e.g. using transfer function analysis (TFA), or wavelet transform analysis). An overview of commonly used CA indices is provided in table 2.1.

Frequency domain methods assume that cerebral autoregulation works as a 'high-pass' filter. In this model, fast, high frequency fluctuations (>0.3 Hz) in ABP (e.g. the beat to beat pulse waveform) are transmitted directly to the cerebral circulation whereas slower, low frequency fluctuations (<0.15 Hz) in ABP are filtered and only partially transmitted to CBF. Transfer function analysis uses the frequency spectra (fast Fourier transform) of the ABP and CBF signals to calculate three parameters (phase, gain, and coherence) in selected frequency bands (usually very low frequency 0.02-0.07 Hz and low frequency 0.07-0.15 Hz)[55]. Phase is the angle of offset (in degrees) between the CBF and the ABP signal and, in essence, represents the 'physiological' timeline by which CBF changes in response to a slow challenge in ABP. A positive phase shift indicates early counter regulatory changes in CBF and intact autoregulation, whereas a phase shift close to zero indicates synchronous timing of changes in the signals and therefore impaired autoregulation. Gain represents the magnitude of transmission of slow waves in ABP to slow waves in CBF (with lower gain probably denoting strong autoregulation – a well-functioning high-pass filter). Finally, coherence represents the statistical association between the two signals. High coherence between ABP and CBF describes a linear system and is an important condition for reliable phase and gain calculation. Because the static autoregulation curve depicted in figure 2.3 is strongly linear below and above the limits of autoregulation, high coherence also can indicate defective autoregulation. For further description of TFA analysis see[56–58].

Cerebral autoregulation can also be estimated in the time domain by correlating slow ABP changes with changes in CBF. For these analyses, ABP and CBF are time-averaged (usually over 10s) to reduce the influence of the cardiac pulse and respiration, and 30 such samples are usually used for a single correlation estimate (Pearson correlation coefficient)[59]. A positive correlation between ABP and CBF indicates impaired autoregulation, whereas a zero or negative correlation indicates preserved autoregulation. The numerical values can be described using different components of the ABP signal: Mx for mean values, Dx for diastolic values, or Sx for systolic values). The utility of correlation-based autoregulation indices in monitoring dynamic trends in autoregulation can be seen in the example of a TBI patient during 'plateau waves' in ICP (figure 2.4). The increases in ICP, and subsequent decrease in CPP produces a decrease in CBF velocity and a profound derangement in the correlation index, Mx (Mx value close to $+1$). After three successive waves of ICP and autoregulation derangement, ICP and Mx return to baseline values. NIRS can also be used for assessment of cerebral autoregulation in the time and frequency domain and is easier to apply in many situations (less operator dependency compared to TCD). NIRS

based autoregulation indices assess the relationship between CPP (or ABP) and NIRS based indices cerebral oxygenation.
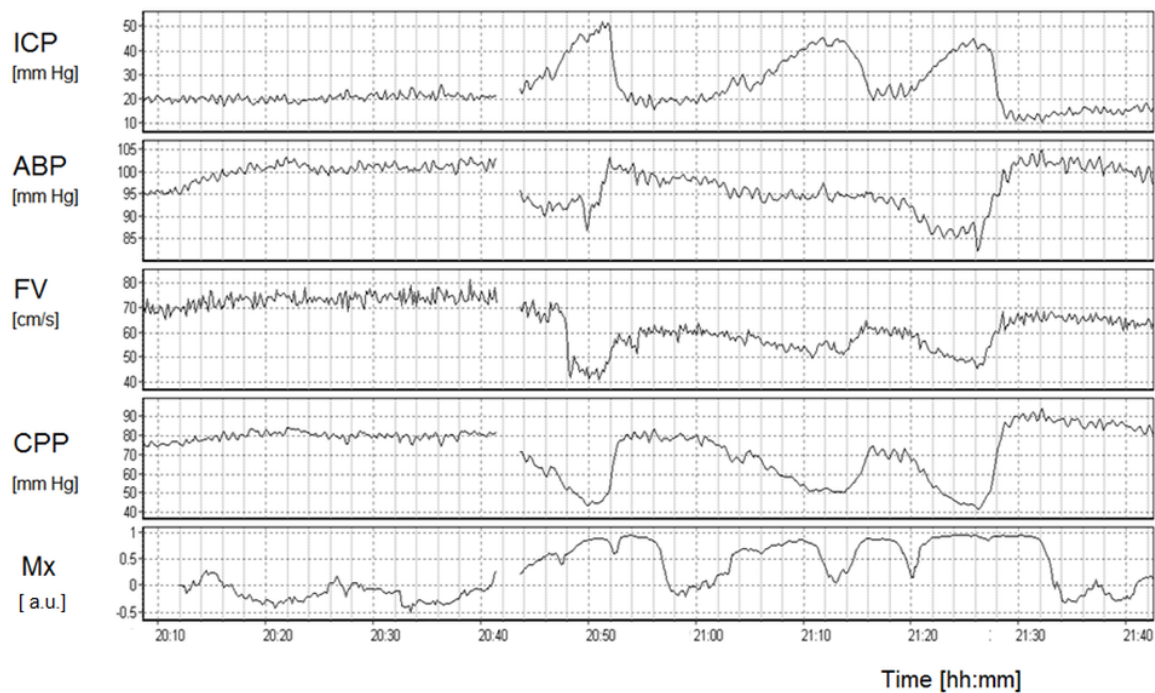
Figure 2.4: **Time-correlation cerebral autoregulation during repeated ICP plateau waves in a traumatic brain injured patient.** The Mx index was calculated continuously (as the Pearson correlation between CPP and MCA flow velocity (FV) over a 300-second moving window) along with other brain modalities (ICP, ABP, FV, CPP). This example demonstrates fluctuations in cerebral autoregulation associated with the three consecutive ICP plateau waves at 20:50, 21:10 and 21:25. The plateaus of such ICP waves are associated with decreases in CPP and FV, as well as transiently impaired cerebral autoregulation. Figure created from clinical monitoring data at Addenbrooke's hospital[60]. *ICP* intracranial pressure; *ABP* arterial blood pressure; *FV* Flow velocity (right middle cerebral artery); *CPP* cerebral perfusion pressure; *Mx* Mean flow index.

The transient hyperaemic response test is an alternative form of cerebral autoregulation test which involves monitoring TCD CBF before during and after a short (5-10s) compression of common carotid artery[61]. With compression, CBF velocity decreases and then increases after release. The reduced CPP during the occlusion provokes vasodilation and therefore the degree of increase in CBF velocity following following release is thought to be a reflection of cerebral autoregulation.

What is the input and what is the output? Dynamic cerebral autoregulation in a strict sense describes the continuous relationship between CPP and CBF. In most clinical applications however, it is not feasible to measure either of these parameters directly and continuously. Especially for bedside measurements, we often accept a compromise;

instead of CPP we measure ABP, instead of CBF we measure CBF velocity and instead of continuous long term recording we allow intermittent (but still continuous) recordings.

Absolute CBF measurement typically requires advanced imaging techniques such as MRI, PET, or duplex ultrasound[62–64]. However, MRI or PET techniques do not allow for continuous monitoring, while duplex volumetric ultrasonography at present does not allow hands-free monitoring (see table 2.1). Due to these limitations, TCD ultrasound is frequently used for bedside assessments of dynamic autoregulation. TCD has an excellent temporal resolution and can relatively easily be applied for short periods of continuous monitoring. A well-documented shortcoming of TCD is that it does not measure volumetric flow because the diameter of the insonated vessel is unknown[38,65]. In the context of cerebral autoregulation measurement, it is usually assumed that the insonated artery (e.g. the middle cerebral artery) does not change diameter significantly during the monitoring period.

A variety of other technologies have been used as indices of CBF. In neurosurgical patients, invasive monitors have been used including jugular bulb cannulation (CBF determined using the Fick principle, see[7]), local blood flow monitors (thermal diffusion–hemadex[66]), and cortical laser Doppler flowmetry[67]. The promising non-invasive technique of near infra-red spectroscopy (NIRS) estimates the local concentration of oxy– and deoxyhaemoglobin (O_2Hb and HHb) continuously in brain parenchyma. Relative changes in the oxyhaemoglobin, deoxyhaemoglobin, and other derived indices (e.g. total oxygenation index) are often used as an indicator of local CBF by assuming constant cerebral oxygen metabolism and systemic oxygenation. Various indices that relate NIRS signals with changes in ABP or CPP have been used as clinical indicators of cerebral autoregulation in cardiopulmonary bypass[68], premature newborns[69], subarachnoid hemorrhage[70] and TBI[71,72] (figure 2.5). In the figure, an increase in ABP seems to drive an increase in CPP associated with a rapid switch from negative to positive values in the autoregulatory index TOx (correlation between total oxygenation index and CPP). TOx then returns to negative values before a profound increase in ICP is again associated with a positive TOx.
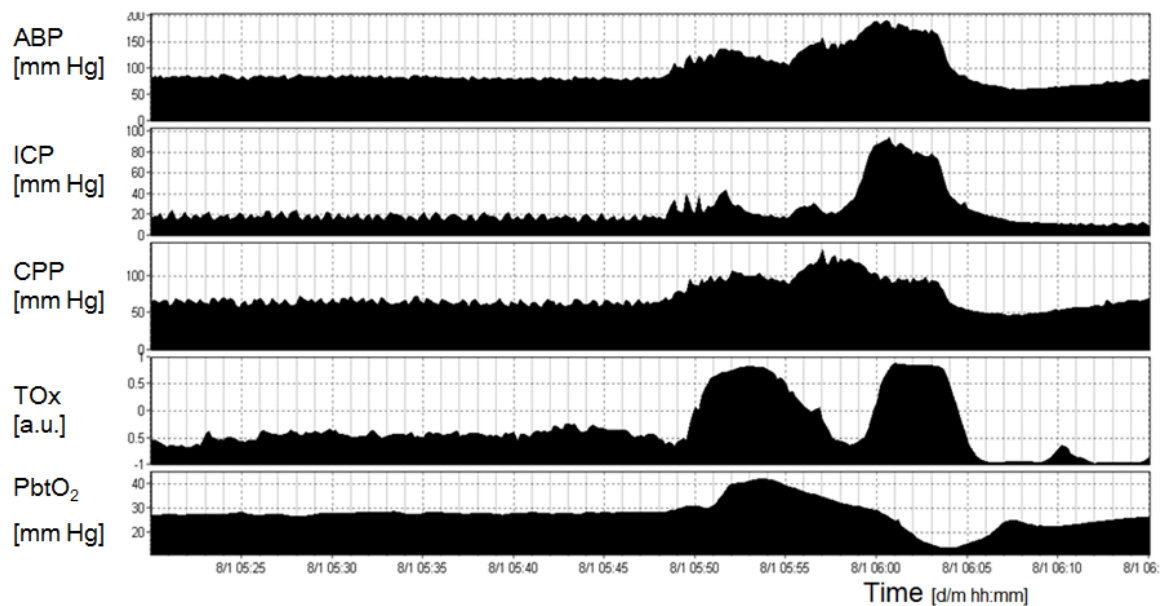
Figure 2.5: **NIRS derived time-domain cerebral autoregulation at the bedside.** This example depicts autoregulation monitoring using NIRS after TBI. TOx is calculated analogously to Mx. It is the moving Pearson correlation between CPP and total oxygenation index (TOI). An increase in ABP produced increase in ICP (probably due to increase in cerebral blood volume) and TOx switched from negative to positive values, indicating a disturbance of autoregulation. NIRS based autoregulation indices offer a non-invasive and potentially continuous option. Figure created from clinical monitoring data at Addenbrooke's hospital[60]. *ABP* arterial blood pressure; *ICP* intracranial pressure; *TOx* total oxygenation index; $P_{BT}O_2$ brain tissue oxygenation.

As discussed earlier, CPP is the pressure gradient driving blood flow to the brain and is generally thought to be equivalent to the difference between ABP and ICP[73]. In many research and clinical settings, we approximate CPP by using only ABP. However in conditions that involve dynamic ICP fluctuations that are independent of ABP (e.g. TBI), approximating CPP with ABP may lead to erroneous autoregulation assessment.

Cerebral autoregulation using two pressures? A related concept to cerebral autoregulation that has proven to be useful in neurosurgical populations is cerebrovascular pressure reactivity. Instead of assessing the relationship between ABP and CBF, cerebrovascular pressure reactivity assesses the relationship between ABP and ICP by taking changes in ICP to represent changes in cerebral blood volume. The underlying physiology of cerebrovascular pressure reactivity in the case of actively autoregulating vessels is as follows: a decrease in cerebral ABP will cause intracranial vessels to dilate[9], which will increase cerebral blood volume. An increase in cerebral blood volume will cause either an increase in ICP (if on the steep portion of the intracranial 'pressure-volume curve') or no change in ICP (if on the flat portion of the pressure-volume curve). Conversely, with defective autoregulation, a decrease in ABP will cause a passive reduction in vessel

diameter, reducing cerebral blood volume and ICP.

These fundamental relationships between ABP, vessel tone, cerebral blood volume and ICP form the basis for the pressure reactivity index (PRx). PRx is analogous to other time-domain autoregulation indices and is calculated as the continuous correlation between 30 consecutive time-averaged (10s) ABP and ICP values (based on[74]). A positive index (positive correlation) implies impaired cerebral autoregulation, whilst a negative (or zero) index (inverse correlation) implies intact autoregulation.

An important consideration of the PRx method is that 'outlier points' of ABP or ICP may disproportionately influence their correlation. The practical manifestation of this is that PRx is an inherently 'noisy' index; this noise may be minimised through time-averaging. Another important property of the PRx is that unlike TCD based measures, it is a continuous (rather than intermittent) measure that can show evolving trends in real-time. The bedside example in figure 2.6 depicts these two properties. In this scenario, a patient, again admitted with TBI, is monitored with continuous ABP, ICP, CPP, and PRx for five days. During the first three days, ICP values are relatively moderate however, PRx becomes consistently impaired as indicated by 'solid red-line' on the trend chart. Four days after initiation of monitoring the patient developed refractory intracranial hypertension. In this case, impaired cerebral reactivity preceded refractory intracranial hypertension.
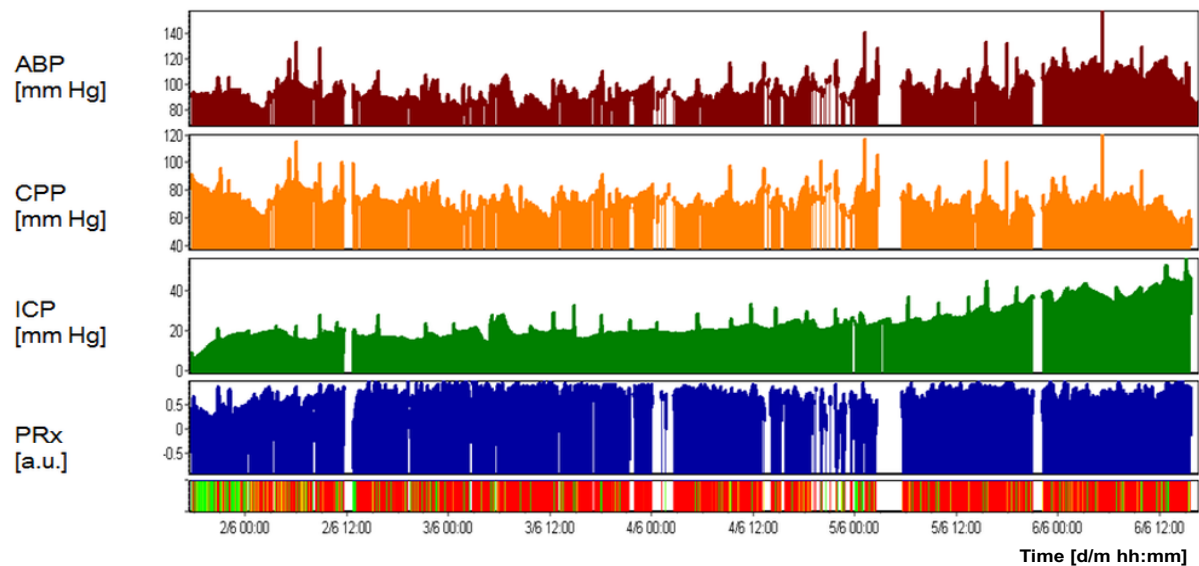
Figure 2.6: **The 'solid red line' disturbance in pressure reactivity index is associated with bad outcome.** This figure demonstrates continuous monitoring of ABP, CPP, ICP, and pressure reactivity (PRx) in patient who after TBI developed refractory intracranial hypertension. A coloured PRx trend chart is shown in the lowest panel (green indicates negative PRx, yellow denotes positive PRx <0.3, and red indicates impaired PRx >0.3). Note that despite relatively moderate ICP values during the first 3 days, PRx is consistently impaired as indicated by 'solid red-line' on the trend chart. Four days after initiation of monitoring the patient developed refractory intracranial hypertension. In this case, impaired cerebral reactivity preceded refractory intracranial hypertension. Impaired PRx is associated with unfavourable outcome[75]. Figure created from clinical monitoring data at Addenbrooke's hospital[46]. *ABP* arterial blood pressure; *CPP* cerebral perfusion pressure; *ICP* intracranial pressure; *PRx* pressure reactivity index.

But can cerebral autoregulation be assessed without measuring CBF? This has been a topic of debate[76,77]. The PRx method presumes a causal relationship between ABP, cerebral blood volume, and ICP. But because the PRx method does not measure CBF or cerebral blood volume, or assess time-delays, this causal relationship will not always be valid; it is prone to confounding by many variables (e.g. changes in intracranial compliance, nursing interventions, changes in sedation and cerebral metabolism). Despite these considerations, PRx provides a continuous, computationally parsimonious, physiologically based assessment of autoregulation that has prognostic relevance (at least in TBI)[74]. Therefore, PRx is probably the best available option to continuously estimate cerebrovascular reactivity over long periods of time in sedated or comatose patients with ICP monitoring[78]. Importantly, as a proof of concept, Brady and colleagues demonstrated in a piglet model that PRx switched from negative to positive values when the lower limit of autoregulation was reached with controlled haemorrhage[79].

In clinical practice, rigid cut-points (i.e. PRx greater than 0), do not always indicate a

CPP below the lower limit of autoregulation, even with time-averaging. However, very often, a 'U-shaped curve' of PRx can be seen[80–82], with the CPP at the lowest value of PRx corresponding to the region of most stable blood flow. Figure 2.7 shows such an example. In this TBI patient blood flow was measured locally (using the thermal diffusion technique), along with ABP, CPP, ICP, and PRx over a period of 10 days. The time-series of these variables is relatively unremarkable (top panel), however when we plot the CPP vs. local CBF we see a striking autoregulatory curve. When perfusion pressures are low there is a passive relationship between cerebral perfusion pressure (CPP) and CBF, when CPP is between 68 and 95 mm Hg, CBF is relatively constant (~40 mm Hg/100g), and when CPP is above 95 mm Hg, CBF is again pressure-passive. When CPP is plotted against PRx we can see a 'U-shaped' curve, with the most negative values of PRx (bottom of the U) corresponding to middle of the 'autoregulatory zone' as indicated by the CPP-CBF relationship. Thus experimental evidence[83], clinical analysis of large cohorts[74,80,81], and individual clinical observations indicate that PRx is a useful indicator of autoregulation.
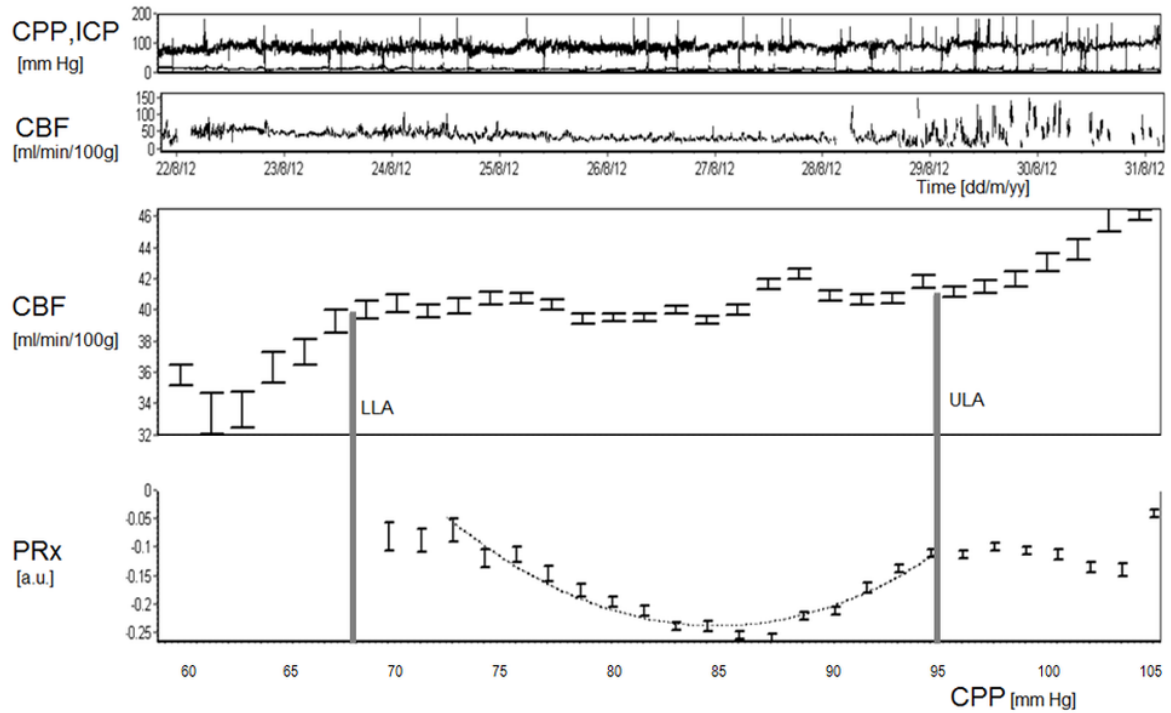
Figure 2.7: **Cerebrovascular pressure reactivity index (PRx) and static autoregulation.** This recording in a severe TBI patient has been made over several days with a hemedex thermal dilution parenchymal CBF monitor. The time-series of CPP and ICP are in the top panel, while the time-series of CBF are in the second panel. The third panel shows mean CBF (with standard error) values plotted in bins of CPP; this shows the classical autoregulation curve. The bottom panel displays the mean PRx values plotted again in bins of CPP; this yields a parabolic, or U-shaped curve. The mid-point of the plateau of the autoregulation curve, and the minimum of the PRx indicate the point of optimal autoregulation – CPP optimal (85 mm Hg). Constructing such parabolic curves forms the basis of CPP-optimal methodology[80,81]. Figure created from clinical monitoring data at Sao Joao hospital, Portugal[46]. *CPP* cerebral perfusion pressure; *ICP* intracranial pressure; *CBF* cerebral blood flow; *PRx* pressure reactivity index; *ULA* upper limit of autoregulation; *LLA* lower limit of autoregulation.

From a critical care perspective, the assessment of cerebral autoregulation can be more practical than monitoring CO_2 reactivity because we can utilise the natural fluctuations of ABP and therefore monitor cerebral autoregulation continuously. Given the heterogeneity of CBF monitoring techniques and the versatility of signal processing techniques, a multitude of 'indices' or metrics of cerebral autoregulation have been proposed. Table 2.3 highlights the rationale of such indices and gives an opinion as to their usefulness.

Table 2.3: Summary of autoregulation indices (continued below)

	Signals required	Calculation
ARI	ABP,Fv	Compares the CBF response to changes in ABP to those predicted from a parametric model with 10 different 'strengths' of autoregulation[48])
Time-domain CBF related (Mx, Sx, Dx, TOx, HVx,COx *et.al.*)	ABP (CPP), and CBF related signal (Fv, TOI, THI)	Pearson correlation between CPP and CBF related signal (300 second window of 10 sec averages). Sx and Dx calculated with systolic and diastolic flow velocity respectively
Frequency-domain CBF related	ABP (CPP) and CBF related signal	Derived from the transfer function of ABP and CBF related signals. Phase is the shift required to align CBF and ABP signals, gain the transmission from ABP to CBF and coherence the statistical association between ABP and CBF
Time-domain ICP (PRx,PAx)	ABP, ICP (or AMP for PAx)	Correlation between 30 consecutive 10 second means of ABP and ICP (AMP for PAx)
Time-domain oxygenation based (ORx)	CPP (ABP), $P_{BT}O_2$	Correlation between 30 consecutive 10 second means of ABP and tissue oxygenation

	Interpretation	Comment
ARI	ARI 0 = absent autoregulation, ARI=9 perfect autoregulation	Moderately complex signal processing required
Time-domain CBF related (Mx, Sx, Dx, TOx, HVx,COx *et.al.*)	Higher value ($\sim$ +1) = impaired autoregulation	Simplistic yet prognostically relevant
Frequency-domain CBF related	Impaired autoregulation = low phase, high gain, high coherence	Moderately complex signal processing. Some prognostic relevance

	Interpretation	Comment
Time-domain ICP (PRx,PAx)	Higher values ($\sim +1$)= impaired autoregulation	Robust measure for long monitoring periods. Simplistic and prognostically relevant. PAx may be superior when intracranial pressure volume curve is flat i.e. at low ICP
Time-domain oxygenation based (ORx)	High ORx ($\sim +1$)= impaired autoregulation	Further validation required

ARI – autoregulation index; CBF- cerebral blood flow; Mx- mean flow index, Dx- diastolic flow index; Sx- systolic flow index; TOx- total oxygenation index; HVx- Haemoglobin volume index; COx- cerebral oximetry index; PRx- pressure reactivity index; ICP- intracranial pressure; PAx- pressure-amplitude index; ORx- oxygen reactivity index; ABP- arterial blood pressure; CPP- cerebral perfusion pressure; Fv-flow velocity; TOI- total oxygenation index; THI-total haemoglobin index; AMP- pulse amplitude of ICP; $P_{BT}O_2$- brain tissue oxygenation.

2.2.4 Neurovascular coupling

The increase in CBF accompanying cerebral cortical activation represents a further way of assessing the reactivity of vessels. Neurovascular coupling can be assessed by using either transcranial Doppler or near infrared spectroscopy to measure the increase in CBF in response to cognitive, emotional, sensory, and motor tasks (for recent review see[25]). Although less studied that pressure or CO_2 reactivity in the TBI or critical care population, neurovascular coupling assessment has potential as it can be assessed non-invasively, repeatedly, and reflects a physiologically distinct aspect of CBF regulation compared with CO_2 or pressure reactivity.

2.3 Clinical applications of bedside assessment of CBF regulation

Using the methodologies described above, the cerebral circulation can be assessed in the severe TBI patient. In this particular setting, techniques such as TCD, NIRS, ICP, and ABP monitoring are desirable as they can provide a continuous assessment of the cerebral circulation without the need for transporting the patient. Unfortunately, validated 'normal' reference ranges are seldom available for the cerebral circulation, and therefore, interpretation must take into account relevant patient comorbidities and the underlying physiologic milieu. Below we summarise the role of the cerebral circulation in TBI, with SAH, stroke, and sepsis for comparison (table 2.5 and 2.6).

Table 2.5: Changes in intracranial physiology in TBI and other critical illnesses

	CBF	CA	CO_2 reactivity	ICP	CPP
TBI	down[84–88] then up[85,87–89]	Impaired[90,91]	down[91–93]	up[94,95]	down[94,95]
SAH	down (vasospasm)[21,96]	Impaired[97,98]	down[96]	up[99,100]	down[100]
Stroke	down[101–103]	Impaired[104,105]	down[106,107]	up[108,109]	-
Sepsis	Unchanged or down[4,110,111]	Unchanged or impaired[111–113]	Unchanged or down[113,114]	-	-

TBI traumatic brain injury; *SAH* subarachnoid haemorrhage; *CBF* cerebral blood flow; *ICP* intracranial pressure; *CPP* cerebral perfusion pressure; *CA* cerebral autoregulation.

Table 2.6: Prognostic relevance of intracranial monitoring parameter

	CBF	CA	CO_2 reactivity	ICP	CPP
TBI	Yes - low[84–86,91] and high[89,91]	Yes[91,115]	Mostly yes[91,93].In some, no[116]	Yes[117]	Yes[117]
SAH	Yes[118]	Yes[118–120]	Yes[121]	Yes[122]	Yes[123]
Stroke	Yes[101,102]	Yes[104]	Yes[106]	Yes[124]	Yes[125]
Sepsis	-	-	-	-	-

Yes indicates that patients with poor outcome have impaired values of the given variable. *TBI- traumatic brain injury; SAH- subarachnoid haemorrhage; CBF- cerebral blood flow; ICP-intracranial pressure; CPP- cerebral perfusion pressure; CA- cerebral autoregulation.*

2.3.1 Traumatic brain injury (TBI)

The pathophysiology of TBI is classically split into two phases with the primary injury occurring at the time of ictus, and secondary injury occurring in the following minutes to days. A cascade of pathophysiologic events leads to deranged cerebral and systemic physiology that add insult to injury; derangement in glucose metabolism, thermoregulation, respiration and cerebral blood circulation all contribute to neuronal injury[14].

The characterisation of the cerebral circulation after severe TBI is not straightforward partly because the disease entity itself is heterogeneous. Despite this diversity, it is clear that in all patients maintaining close attention to cerebral perfusion is essential. The

cerebral circulation is universally compromised after severe TBI; CBF, CO_2 reactivity and cerebral pressure autoregulation can all be impaired at various stages (table 2.5). Low CBF[84–86,91], high CBF[89,91] and impaired autoregulation[74,115] have all been associated with worse outcome.

CO_2 reactivity after TBI

Experimental studies reveal impaired CO_2 reactivity after severe TBI[126,127]. Impaired CO_2 reactivity has been shown to be related to unfavourable outcome in some studies[93,128], however this is not universal[116]. Carmona Sauzo and colleagues, used parenchymal brain tissue oxygen monitors to assess CBF in 90 TBI patients and found that while all patients seemed to have a low CO_2 reactivity on day one, this gradually improved over the first 5 days of monitoring. Interestingly, CO_2 reactivity on day 5 was higher in those with unfavourable outcome[116]. Unfortunately, a low sample size (n=10 by day 5 of monitoring), and the potential for confounding changes in CPP make the generalizability of this surprising result uncertain.

Pressure autoregulation after TBI

Experimental evidence from porcine and rodent models indicate that TBI directly impairs cerebral autoregulation[90,129–131], however, the timing and methods of autoregulation measurement are important considerations as other studies have not found autoregulation impairment[132,133]. The cause of impaired cerebral autoregulation after TBI is unclear but likely multifactorial given that any given TBI patient can have a multitude of prehospital haemodynamic injuries and diverse vascular abnormalities on brain imaging. For example, some patients have follow-up CT scans with extradural haematomas, demarcated contusions, and diffuse swelling whilst others may have normal CT scans but elaborate signs of diffuse axonal injury (microbleeds) on specific MRI sequences. Others present with complicating circumstances like hypotension and hypoxia at the scene, or concomitant injuries such as severe heart and lung contusions that require specific management. Not surprisingly, given this complexity, the relative contributions of these processes to impairment of cerebral autoregulation are unclear.

Interpretation of an autoregulation measurement after TBI requires careful consideration; one must consider not only the presenting cerebral and extracerebral injury, but also the current therapeutic management. Management of TBI patients often requires hypocapnia, sedation, vasopressor support and multiple other medications, all of which can alter autoregulation. In addition, timing since injury seems to be important because autoregulation impairment after TBI appears to be time dependent[59]. Clearly, an assessment of autoregulation needs to be considered in the context of the physiologic, pharmacologic, and pathologic milieu of the individual patient.

Cerebral autoregulation in the acute phase has been associated with patient prognosis after severe TBI[134]. Both intermittent and continuous methods of cerebral autoregulation

assessment have demonstrated that impaired cerebral autoregulation is related to worse patient outcome (reviewed in[75,135]). For PRx, a threshold of PRx = 0.25 a.u. was most strongly associated with mortality and for Mx a threshold of 0.30 was proposed. The proportion of severe TBI patients who develop impaired cerebral autoregulation is not known.

CPP and ICP after TBI

ICP remains one of the critical concerns in the acute period after TBI and ICP monitoring is recommended in order to reduce in-hospital and 2-week post-injury mortality[134]. Experimental evidence confirms that TBI causes an increase in ICP within 24 hours[94]. Increased ICP is related to adverse patient outcome[136], perhaps as patients who die often have refractory intracranial hypertension and subsequent herniation or depressed CBF. However, similar to impaired autoregulation, the proportion of severe TBI patients in which raised ICP is a problem is unknown.

Further, what even constitutes a pathologically raised ICP is unclear; in some situations such as idiopathic intracranial hypertension or CSF infusion studies in hydrocephalic patients, ICP values above 40 mm Hg can be tolerated without symptoms or apparent pathological consequences. After TBI, levels significantly lower than this are probably harmful due to the presence of pressure gradients, cardiovascular co-morbidity, and impaired vascular function. In addition, whether a particular value of ICP has a pathological effect probably also depends on the duration of the episode, as well as the prevailing CPP and autoregulation status[137,138]. Aside from individual examples (figure 2.6), the effect of raised ICP and depressed CPP on other monitored parameters such as brain oxygenation or dynamic autoregulation is unknown.

Because elevated ICP can depress CBF through a decrease in CPP (figure 2.1), a strategy promulgated in the early 1990's (and still common today) is to bolster CPP using vasopressors such as noradrenaline[139]. Although initial results were promising[139], a randomised controlled trial found no outcome benefit of a management strategy based on maintaining CBF using a CPP targeted protocol, compared with maintaining ICP below 20 mm Hg[140]. In fact, in that study, those in the group with CPP augmentation developed higher rates of acute respiratory lung disease[140].

A recent randomised controlled trial compared an ICP monitoring based management protocol with an imaging based protocol after severe TBI and found no significant differences in patient outcome, both in terms of mortality and functional outcome[141]. This trial was conducted in centres previously naïve to ICP monitoring in Bolivia and Ecuador. The trial was tightly controlled with patient management for both the ICP group and the imaging group being protocolized. Thus, the study provides some evidence that a management protocol based on ICP monitoring does not lead to improved outcomes amongst hospitals unfamiliar with ICP monitoring.

However, some retrospective studies provide indirect support for ICP monitoring.

Gerber and colleagues compared mortality and ICP monitoring trends over a 10 year period and observed a decreased mortality coinciding with increased rates of ICP monitoring[142]. Similarly, mortality has been demonstrated to be lower in those with ICP monitoring in two further studies[143,144].

Given that cerebral haemodynamics after TBI seem to show a distinct time evolution[85,145], it is clear that defining an optimal CBF is problematic as it is likely to vary with the patients' individual physiologic milieu, as well as the temporal evolution of disease. Furthermore, continuous measurements of CBF, although possible, are seldom feasible (table 2.1) and therefore ICU protocols commonly dictate not CBF *per se* but a target range of CPP. In this regard, individually optimising CPP to a continuously calculated measure of vascular function such as PRx seems promising. The CPP dependence of PRx can be used to asses at which CPP the autoregulation is most efficient (i.e. the CPP at which the PRx is most negative; figures 2.7 and 2.8). This is important because CPP is a variable (unlike CBF or indices of autoregulation) that can be titrated precisely at the bedside. Importantly, the difference between CPP and the optimal CPP has been shown to be relate to outcome[80,81].

Figure 2.8 demonstrates long-term continuous monitoring of cerebral autoregulation using PRx in a TBI patient. In this case, ICP was initially above 20 mm Hg and then subsided. The CPP varied between 60 and 100 mm Hg and when this CPP was plotted against PRx, a U-shaped, parabolic curve is observed with a minimum at ~90 mm Hg.
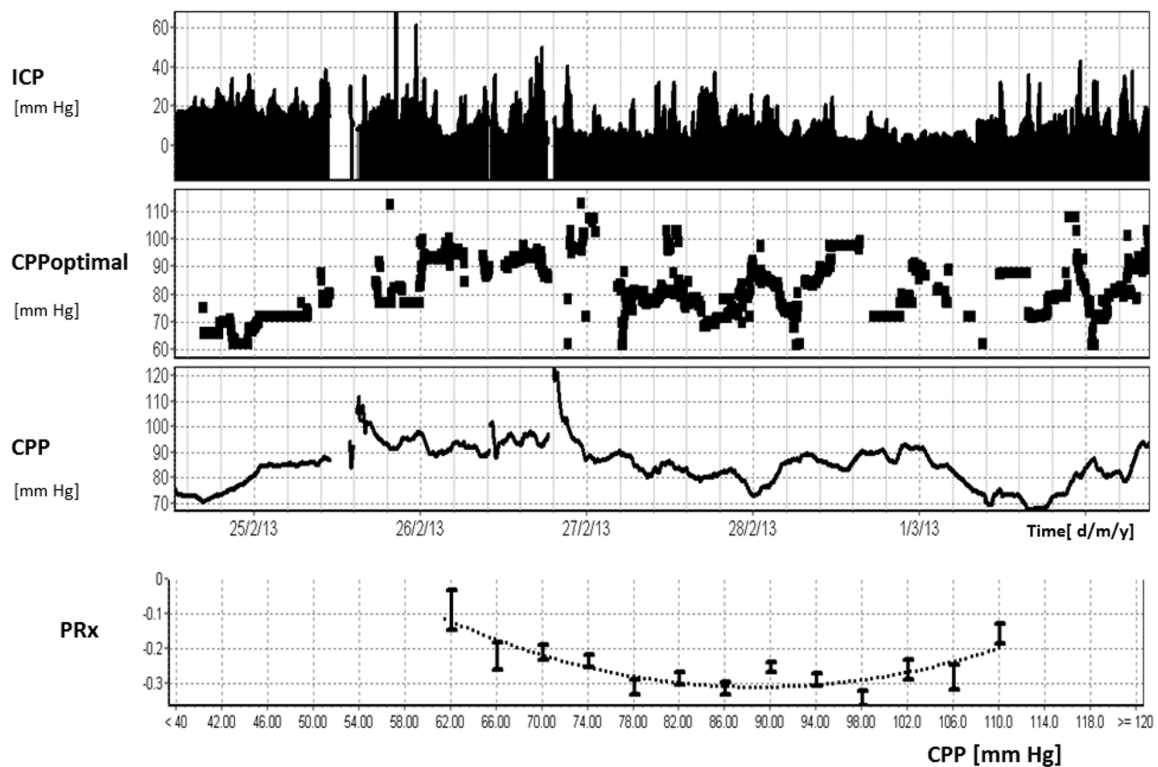
Figure 2.8: **Long-term monitoring of pressure reactivity (PRx) in a patient after TBI.** ICP was first elevated to 20 mm Hg, then decreased, showing some fluctuations over 7 days of monitoring. PRx had a parabolic distribution along recorded range of CPP (from 60 to 100 mm Hg). The minimum of this parabola indicates 'optimal CPP' from the whole 7 days period (90 mm Hg in this case – as compared to above 65-70 mm Hg, advised by guidelines- which illustrates well that CPP-oriented management must be individualized- it is not true that one shoe size is good for everybody). Moreover, such a fitting of an 'optimal curve' may be repeated in time, based on data from the past 4 hours. This enables prospective detection and tracing of 'optimal CPP' and targeting current CPP to the optimal value, which may change in a course of intensive care. Figure created from clinical monitoring data at Addenbrooke's hospital[46]. *ICP* intracranial pressure; *CPP* cerebral perfusion pressure; *PRx* pressure reactivity index.

2.4 Summary of evidence

With the increasing availability of bedside physiology monitors and sophisticated online analysis software, large-scale integrated interrogations of CBF regulation are now possible. One important research theme is developing robust prediction tools based of cerebral physiologic monitoring for critically-ill TBI patients. Accurate prognosis is of obvious importance for patients, families and clinicians alike, but current methodologies have some limitations. For example, prognostic tools in TBI use clinical, laboratory and radiographic features on admission to predict patient outcome[146]. However, some of the input variables

are open to interpretation (e.g. the grading of a CT scan), and prognosis should ideally be updated based on clinical and physiological developments. In this sense, prognostic tools that update risk estimates based on online monitoring of CBF regulation could facilitate clinical decision making.

As alluded to above, there is a distinct paucity of data in several key areas regarding intracranial haemodynamic monitoring after severe TBI. The prevalence of secondary injuries due to derangement in monitored parameters such as ICP, CPP or PRx is uncertain. Further, how intracranial haemodynamic monitoring is affected by changes in management protocols has not been elucidated. Risk factors for, and sequelae from increased ICP or impaired autoregulation also remain to be fully described. Finally, attempts at integrating the various aspects of intracranial haemodynamic monitoring to form a consistent patient therapy remain preliminary, but paradigms such as "CPPopt" deserve further exploration.

With such a research focus on characterizing brain function in health, it is a sad fact that in most cases, our ability to monitor brain function and the cerebral circulation in the critically ill patient is rudimentary. Recent Neurocritical Care Society guidelines attempt to correct this situation[78]. With the maxim "time is brain", a renewed focus on high fidelity cerebrovascular monitoring is required – irreversible cerebral ischaemia can occur in a matter of minutes.

To date, there is no randomised trial showing that intracranial haemodynamic monitoring improves outcome after TBI. Progress in the neurocritical care of TBI will probably also depend on moving away from broad assumptions or 'one size fits all' physiological targets; each patient brings a different physiology which should be catered for. Using continuous markers of vascular function has the potential to optimise therapy to the individual patients need. With the sophistication of signal processing and bioinformatic tools increasing exponentially, the challenge lies in successful integration of cerebral circulation monitoring paradigms at the bedside.

In the following chapters, I outline the methods used for this thesis (chapter 3), the prevalence of intracranial haemodynamic monitoring secondary insults after TBI and their responsiveness to changes in management paradigms (chapter 4), risk factors and sequelae of raised ICP (chapter 5 and 6), before exploring novel applications of intracranial monitoring in TBI (chapter 7).

Chapter 3

Methods

While each of the 8 studies detailed in this thesis are described within their corresponding chapter, there are significant overlaps in many of the methodological aspects across the studies. 6 of the studies were performed from a prospectively collected adult TBI database, 1 from a paediatric TBI database and 1 from previously collected experimental data. Common methods across the 6 adult TBI studies are described below.

3.1 Patients

The data used in the 6 adult TBI studies comprising this thesis was gathered from sub selections of patients from a database of patients admitted to the Addenbrooke's Hospital Neurocritical Care Unit between 1991 and 2017. In total 1146 TBI patients with a clinical need for intracranial pressure monitoring and computerized signal recordings were included in the database. The computerized data storage protocol was reviewed and approved by the local ethics committee of Addenbrooke's Hospital, Cambridge University and the neuro critical care unit User's Group. The study was approved by the institutional ethics committee (30 REC 97/291).

Inclusion criteria were: TBI; invasive monitoring of ICP and ABP for at least 12 hours, admission Glasgow Coma Scale (GCS) and mortality data available. While some patients in the cohort would be categorized into the moderate TBI group on basis of initial GCS, these patients deteriorated and subsequently required invasive intracranial monitoring and therefore were included in the analyses. Patients were managed according to contemporaneous TBI guidelines. Between 1991 and 1993, patients were managed within the Department of Neurosurgery and general Intensive Care Unit if ventilatory or organ support was needed. A dedicated 12 bed Neurocritical Care Unit was opened in 1994 which was later expanded to 21 beds in 2010 followed by transformation to a major trauma unit and further expansion to 23 beds in 2011.

A protocol aimed at keeping ICP < 20 mm Hg and CPP > 70 mm Hg using step-wise medical and surgical management was implemented in 1994. In 2003, modifications to ICP and CPP targets were introduced (reduction of CPP target to CPP > 60 mm Hg) followed

by restricting hyperventilation (end-tidal pCO_2 range adjusted from 4-4.5 kPa to 4.5-5 kPa). Introduction of multimodal monitoring including microdialysis and brain tissue oxygenation ($P_{BT}O_2$) occurred in 2002 and 2004 respectively. Assessment of the PRx was a part of multimodal monitoring since 1996, however, it was included in clinical assessment (to assist with prognostication) of TBI in 1999. Furthermore, since 2012, autoregulation based CPP targets have been available to try to optimize management as a secondary parameter at the clinicians discretion. In 2015, blood pressure zeroing was changed from the level of the right atrium to the level of foramen of Monro leading to a general change in the ABP and CPP levels by approximately 10 mm Hg.

All patients were sedated, intubated, and ventilated. The step-wise ICP management included positioning and head elevation, prevention of hypotension and hypoxia and maintenance of end-tidal pCO_2 levels, sedation, muscle paralysis, ventriculostomy, osmotic agents, induced hypothermia, barbiturate coma and decompressive craniectomy. CPP was maintained at target levels using intravenous fluids, vasopressors and inotropes. Glucose control was achieved with insulin sliding scale, with target blood glucose levels of between 6 and 8 mmol/L. Seizure management was achieved using phenytoin and levetiracetam as appropriate. Initial Glasgow Coma Scale was obtained for each patient pre sedation. Patients without eye, vocal and motor score from the GCS were included because data for patients before electronic medical records frequently had only total GCS score. Glasgow outcome score was obtained at 6 month post injury (1=dead, 2= vegetative state, 3= severe disability, 4 = moderate disability, 5= good recovery).

3.2   Data acquisition and processing

ICP was monitored with an intraparenchymal microsensor inserted into the frontal cortex (Codman ICP MicroSensor, Codman & Shurtleff, Raynham, MA) and arterial blood pressure was monitored in the radial or femoral artery (Baxter Healthcare CA, USA; Sidcup, UK) with a zero calibration at the level of the right atrium (1992-2015) and at the foramen of Monro (2015-2017). Between 1992 and 1996 data trends (one-minute time averages) were collected with non-propriety software developed in-house. From 1996-2002 data were sampled at between 100 Hz with proprietary data acquisition software (ICM) and one-minute trends were stored. From 2002 -2017 data were collected using ICM+©, (Cambridge Enterprise, Cambridge, UK-`http://www.neurosurg.cam.ac.uk/icmplus`). PRx was able to be calculated from 1996 onwards. PRx was calculated as the Pearson correlation of 30 consecutive 10-second average values of ABP and ICP. CPP was calculated as ABP- ICP. A 10-second average was used to reduce the influence of respiratory and pulse waveforms. A 300-second moving window was used to generate continuous PRx values. Comma separated value files for each patients minute-by-minute data were imported into the software R for generation of patient summary data[147].

3.3 Statistical analyses

Data are presented as means ± standard deviation (sd). For analysis of the relationship with outcome, generalised linear models (binary logistic) were created to predict either mortality or unfavourable outcome (severe disability, vegetative state or death). For multivariable models, the best subset selection algorithm was applied using an exhaustive method that searches the best model, based on the lowest Akaike Information Criterion (AIC)[148]. All statistical analyses and visualisations were performed on R statistical software[147], with the following packages: dplyr[149], ggplot2[150].

Chapter 4

ICP, CPP, and cerebral autoregulation monitoring after traumatic brain injury

This chapter is based on data presented at the International Neurotrauma Society conference in Capetown 2016:

- Donnelly, J., Czosnyka, M., Adams, H., Kolias, A., Aries, M., Smielewski, P., Hutchinson, P.J.A., Menon, D.K., Pickard, J.D. and Budohoski, K.P., 2016, February. 20 years of ICP monitoring in traumatic brain injury- single centre experience from Cambridge- UK. Journal of Neurotrauma (Vol. 33, No. 3, pp. A31-A31).

4.1 Secondary insults prevalence, co-occurrence and relationship with outcome after severe TBI

4.1.1 Introduction

Stabilising CBF, and preventing raised ICP are two important aims of the neurocritical care of severe TBI[78]. The stability of CBF will in turn depend on many factors including the carbon dioxide, temperature, ABP, ICP, and CPP[17]. Of these factors, the stability of CBF in the face of changes in CPP - cerebral autoregulation - is often disturbed after TBI[90,129–131]. This, combined with current limitations of continuous CBF monitoring means that CPP monitoring (and therapy) forms a core component of care after severe TBI[134]. ICP is also often monitored after TBI on the basis that it is increased after experimental TBI[94], it contributes to decreased CPP and can serve as warning for evolving intracranial pathophysiology[151]. Whereas ICP and CPP monitoring are widely implemented after severe TBI, cerebral autoregulation monitoring has been predominantly restricted to clinical research settings.

The combination of continuous ICP, CPP and cerebral autoregulation monitoring therefore has the possibility of allowing a detailed overview of intracranial physiology[58,82]. Despite the theoretical rationale for such monitoring in TBI, several issues will need to be clarified to support a more widespread implementation. First, the proportion of patients that experience impairment in ICP, CPP or CA has not been established. Second, the co-occurrence of insults due to impaired ICP, CPP or cerebral autoregulation is unknown. Finally, whether incorporating knowledge of cerebral autoregulation to the more traditional ICP and CPP monitoring data adds useful information on the patients' physiological state is unclear.

In this descriptive study we focus on secondary injuries due to high ICP, low CPP, and impaired cerebral autoregulation describing their 1) incidence after severe TBI 2) co-occurrence, and 3) prognostic importance.

4.1.2 Methods

Patients

822 severe TBI patients entering the neurocritical care unit (NCCU) with computerized ICP monitoring (September 1996 - January 2017) were selected. Regional ethical approval was obtained (30 REC 97/291) for anonymised data recording. Patients were managed according to TBI guidelines[14] aimed at keeping ICP < 20 mm Hg and CPP > 50-60 mm Hg. CPPopt or PRx-guided management was not part of the management algorithm. GOS was obtained at 6 months by outpatient assessment, with the following categories: good recovery, moderate disability, severe disability, vegetative state, death[152]. Unfavourable outcome was defined as severe disability, vegetative state, or death.

Data Acquisition and Processing

ICP was monitored with an intraparenchymal sensor (Codman ICP Micro- Sensor, Codman & Shurtleff, Raynham, MA). Arterial blood pressure (ABP) was zeroed at the level of the right atrium before 2015 and at the level of the external acoustic meatus thereafter (Baxter Health- care CA, USA; Sidcup, UK). After 2015, corrections were made for hydrostatic pressure influence during changes in patient position, whereas before 2015, no such adjustments were made. Data were sampled at 100 Hz with proprietary data acquisition and analysis software (ICM+©, `http://www.neurosurg.cam.ac.uk/icmplus`). ABP and ICP signals were first averaged (mean) over a 10-second window then PRx was calculated as the moving Pearson correlation of 30 consecutive ABP and ICP, updated every minute.

Hourly averages of ICP, PRx and CPP were calculated. The incidence of significant secondary insults due to ICP, PRx, and CPP were defined as having at least 1 hour with a mean value above (or below for CPP) the respective threshold (ICP 20, CPP 60, and PRx 0.25)[136]. The co-occurrence of insults due to ICP, CPP and PRx were visualised using a Euler diagram depicting the hours in each of the 7 states possible from the intersection of these three variables (impaired ICP only, impaired CPP only, impaired PRx only, impaired ICP and PRx, impaired ICP and CPP, impaired CPP and PRx, impaired ICP CPP and PRx).

Statistical analysis

Data are reported as means and standard deviations. Univariate generalised linear models were used to assess the influence on outcome of %time spent in each of the 7 states of the euler diagram. Multivariable generalised linear models including GCS and age were used to assess the adjusted prognostic influence of %time spent in each of the 7 states of the euler diagram. To reach the most parsimonious model, the best subset selection algorithm was applied, which uses an exhaustive method that searches the best model based on the lowest Akaike Information Criterion (AIC)[153]. We used the R language and software environment for statistical computation (R Core Team 2015 version 2.12.1)[154] using the following packages: eulerr[155] dplyr[149], ggplot2[150], bestglm[148]. The significance level was set at 0.05.

4.1.3   Results

822 patients were included in the current analysis with a mean age of 39.3 (table 4.1). 643 were male and the majority 598 were severely injured on initial GCS assessment. The remainder had a secondary neurological deterioration. 467 ended up with unfavorable outcome (56.81%), while 185 (22.51%) died. The mean duration of monitoring was 130.99 (sd 108.49) hours.

Table 4.1: Patient demographics; secondary insults co-occurrence after TBI

	Overall
n	822
GOS (%)	
D	185 (22.5)
VS	14 (1.7)
SD	268 (32.6)
MD	204 (24.8)
GR	151 (18.4)
Age [years] (mean (sd))	39.30 (17.18)
Sex = male (%)	643 (78.2)
GCS <= 8 (%)	
FALSE	216 (26.3)
TRUE	598 (72.7)
NA	8 (1.0)
Decompressive craniectomy (%)	
FALSE	456 (55.5)
TRUE	183 (22.3)
NA	183 (22.3)
ICP [mm Hg] (mean (sd))	15.13 (7.48)
CPP [mm Hg] (mean (sd))	78.21 (9.06)
PRx [a.u.] (mean (sd))	0.07 (0.17)
ICP >20 mm Hg > 1 hour = yes (%)	623 (75.8)
ICP >40 mm Hg > 1 hour = yes (%)	93 (11.3)
CPP <60 mm Hg > 1 hour = yes (%)	452 (55.0)
CPP <50 mm Hg > 1 hour = yes (%)	134 (16.3)
PRx >0.25 a.u. > 1 hour = yes (%)	754 (91.7)
% time ICP > 20 mm Hg (mean (sd))	21.84 (27.16)
% time CPP < 60 mm Hg (mean (sd))	4.45 (11.75)
% time PRx > 0.25 a.u. (mean (sd))	24.19 (22.72)
% time CPP, ICP and PRx impaired (mean (sd))	1.92 (8.64)
% time ICP and PRx impaired (mean (sd))	6.84 (15.11)
% time CPP and PRx impaired (mean (sd))	2.66 (9.40)
% time CPP and ICP impaired (mean (sd))	2.83 (10.59)
% time CPP, ICP and PRx not impaired (mean (sd))	59.92 (27.40)

GOS Glasgow outcome score; *ICP* intracranial pressure; *CPP* cerebral perfusion pressure; *PRx* pressure reactivity index.

Of the 822, 623 (75.79%) had a mean hourly ICP greater than 20 mm Hg for at least one hour and this percentage was the highest in the group who died (151 (81.62%)). 93 (11.31%) had severe intracranial hypertension (ICP >40 mm Hg for at least an hour). A low CPP (<60 mm Hg) for at least one hour occurred in 452 (54.99%) patients and occurred the most often in patients who died (n=123 (66.49%)). The number of patients with sustained (1 hour) impaired PRx was 754 (91.73%) and this number was relatively higher in those that died (176 (95.14%)).

The co-occurrence of the impairments of different combinations of ICP, CPP and PRx across the entire cohort data is visualised in a euler diagram (figure 4.1), in which the relative size of the circle indicates the amount of time (hours) spent in each state of physiological impairment. PRx and ICP impairments were both more common than CPP impairments and although there was significant overlap between impairment in all three variables, there were also large amounts of time where insults (ICP or PRx) occurred independently of each other. A numerical summary of the relative time in each state is shown in appendix A, table A.1.

To compare the impact of physiological insults in each of the seven states outlined in section 4.1, univariate odds ratios were constructed for the association of %time in each particular state with patient outcome (mortality or unfavourable outcome). Using this approach it is clear that states with co-occurring impairments had a stronger relationship (higher odds ratio) with outcome than when only a single facet of physiology was impaired. (figure 4.2).
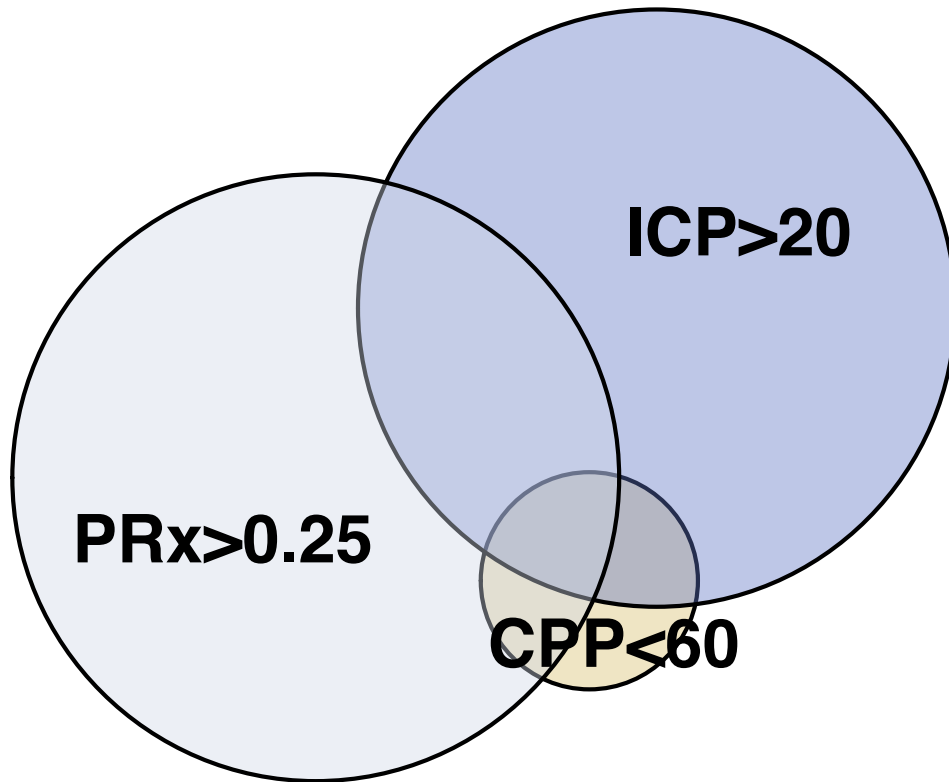
Figure 4.1: **Euler diagram of hours spent with secondary insults due to high ICP (ICP> 20 mm Hg), low CPP (CPP < 60 mm Hg), and impaired PRx (PRx > 0.25) for entire cohort (n=822)**. The area of each of the 7 unique sections of the euler diagram corresponds to the relative number of hours in each adverse physiological condition. The majority of CPP insults were associated with impaired PRx or ICP. In contrast, the majority of ICP or PRx insults were isolated, i.e. without concomitant derangement in the other 2 physiological parameters. *ICP* intracranial pressure; *CPP* cerebral perfusion pressure; *PRx* pressure reactivity index.
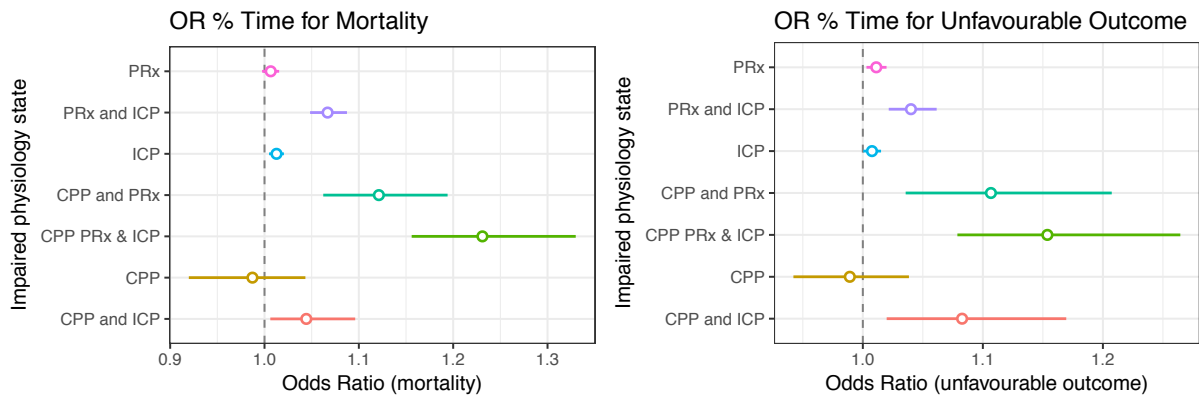
Figure 4.2: **Univariate odds ratio (95% confidence interval) of percentage time in each impaired physiological state for predicting unfavourable outcome (left) and mortality (right).** In both cases, ICP or CPP insults associated with impaired PRx denoted more extreme odds ratios than ICP insults associated with preserved PRx. This highlights the importance of considering cerebral autoregulation (PRx) when interpreting secondary insults due to ICP or CPP. *OR* odds ratio; *PRx* pressure reactivity index; *ICP* intracranial pressure; *CPP* cerebral perfusion pressure.

Physiological insults from the univariate analysis (figure 4.2) were added to a multi-variable outcome prediction model (one for unfavourable and one for mortality) with the addition of static variables (age, initial GCS). In both models, combined impairments (ICP and PRx, CPP and PRx, CPP and PRx and ICP) and single parameter impairments (ICP, PRx) were included in the final models, while in the unfavourable outcome model impaired CPP and ICP was additionally included (table 4.2).

Table 4.2: Odds ratios and *summary statistics* from multivariable analyses; secondary insults co-occurrence after TBI

Statistic	Mortality	Mortality p-value	Unfavourable outcome	Unfavourable p-value
Intercept (OR)	0.03 (0.01-0.07)	<2e-16	0.75 (0.44-1.27)	0.283
Age (OR)	1.05 (1.04-1.06)	2e-13	1.03 (1.02-1.05)	1e-11
GCS (OR)	0.86 (0.8-0.91)	3e-06	0.82 (0.78-0.86)	2e-15
%time PRx >0.25 (OR)	1.01 (1-1.02)	0.027	1.01 (1-1.02)	0.029
%time ICP>20 (OR)	1.02 (1.01-1.03)	6e-05	1.01 (1-1.02)	0.009
%time CPP<60 & ICP >20 (OR)			1.04 (0.99-1.13)	0.224
%time CPP<60 & PRx >0.25 (OR)	1.1 (1.04-1.17)	0.002	1.09 (1.01-1.19)	0.039
%time ICP>20 & PRx >0.25 (OR)	1.05 (1.03-1.07)	1e-05	1.02 (1-1.04)	0.036
CPP <60 & PRx >0.25 (OR)	1.18 (1.11-1.28)	1e-06	1.09 (1.03-1.2)	0.022
AIC	*649.14*		*957.39*	
Log-Likelihood ratio	*-316.57*		*-469.69*	

OR odds ratio; *GCS* Glasgow coma score; *ICP* intracranial pressure; *CPP* cerebral perfusion pressure; *PRx* pressure reactivity index.

4.1.4 Discussion

Using a comparatively large severe TBI neuromonitoring database we describe the high incidence of ICP (76%) and autoregulation (92%) secondary insults and a relatively lower incidence of insults due to CPP (55%). Although some of these insults occurred at the same time, the majority occurred independent of each other. Finally, an ICP or CPP insult was more damaging if it was associated with impaired compared with intact autoregulation. Together these data highlight the pervasiveness of cerebral insults after TBI and the potential added value of autoregulation monitoring in interpreting a ICP or CPP insult.

ICP secondary insults

Sustained ICP insults (greater than 20 mm Hg) occurred in over three-quarters of the cohort. Although the definition of an ICP insult (greater than 20 mm Hg for more 1 hour) is somewhat arbitrary, it fits with recent analytical studies indicating that ICP > 20 for an hour is associated with poorer outcome[137], and also with clinical guidelines which advocate treatment when ICP is above ~ 20 mm Hg[134]. What makes some patients vulnerable to increases in ICP and others more resistant is unclear and likely complex considering that ICP increases can occur with an increase in volume of any of the blood, parenchymal, or CSF compartment after TBI.

Whatever the cause, raised ICP after TBI is deleterious because it affects cerebral metabolism, cerebral haemodynamics and can even have systemic effects[156,157]. Because ICP can be monitored, and modulated, ICP has become a standard of care in the management of severe TBI[134]. Despite this, there is conflicting evidence with regards to the importance of ICP insults and therefore ICP monitoring in general. As discussed in section 2.3.1, a randomised controlled trial (the BEST TRIP trial) that compared a protocol based on ICP monitoring, with a protocol based on imaging and clinical assessment of ICP, found no significant differences in patient outcome[158]. Similarly, two other trials found that although ICP therapies (early implementation of hypothermia or primary decompressive craniectomy respectively) were effective in decreasing ICP, they did not improve patient outcomes[159,160]. The lack of prognostic improvement despite improvements in ICP highlights the important fact that current treatments to decrease ICP are not without side-effects and therefore the timing and indications for therapy must be carefully considered. In contrast to these three negative studies, the RESCUEicp trial found that in patients with secondary severe intracranial hypertension, decompressive craniectomy decreased mortality compared to a medical alternative (barbiturate coma)[161]

CPP secondary insults

CPP insults in this cohort were less common than ICP or PRx insults with just over half of patients having an average CPP <60 mm Hg for at least one hour. The relatively low (compared to PRx and ICP) prevalence is probably because CPP can be more readily

modulated by increasing the dose of vasopressors. Time with impaired CPP was not significant on multivariable modelling highlighting the fact that a low CPP alone may not be detrimental. Interestingly, low CPP was often (~ three-quarters of the time) associated with an increased ICP or impaired PRx (figure 4.1 and table A.1).

The concept of CPP as the difference between ABP and ICP has had significant implications for TBI management. In TBI, where raised ICP is a prevalent problem, one way of ensuring the brain has an adequate perfusion pressure and thus cerebral blood flow is by pharmacologically increasing ABP. This lead to the CPP oriented protocols of Rosner where CPP was increased to relatively high values[139]. Vigorous CPP targeting with vasopressors can however have negative effects with myocardial and pulmonary dysfunction common[140].

Autoregulation secondary insults

Autoregulation impairment was common in this cohort with ~ 90% of patients experiencing at least 1 hour of impaired PRx (table 4.1). As expected, we found that impaired PRx potentiated the effect of a high ICP or a low CPP (figure 4.2). However, impaired PRx alone (i.e. with preserved CPP and ICP) also had a significant effect on patient outcome after multivariable adjustment. This hints that PRx may have some additional prognostic information even if perfusion pressure and ICP are stable.

The causes and consequences of impaired PRx after TBI are uncertain. The impairment could stem from the injury itself, or could be related to changes in blood gases, temperature, or medication[162,163]. Impaired PRx potentially causes regional microvascular damage from passive transmission of ABP slow waves to ICP and through this mechanism may have a significant effect on patient outcome. In addition, it has recently been demonstrated that PRx is strongly related to the phase-shift between the ICP and ABP signals such that with a PRx close to $+ 1$, slow ABP and ICP changes will be occurring at the same time[164]. Whether the poor prognosis associated with disturbed PRx is due to the transmission of ABP waves to cerebral blood volume *per se*, or a more general reflection of a disturbed cerebrovascular system is unknown.

In contrast to ICP after TBI, no randomised controlled trials have been performed on cerebral autoregulation based treatments. This is in part due to a lack of standardised methods of how to assess it, and in part due to the lack of knowledge of how to efficiently treat it. The pressure reactivity index is perhaps the most widely studied autoregulation monitoring method in severe TBI but as discussed in 2.2.3, PRx is an *indirect* estimate of cerebral autoregulation. Further the exact cut-off between intact and impaired values is not resolved with values between 0 and 0.3 being proposed (PRx of 0.25 was chosen for this study as it was shown to correlate the most strongly with mortality in the severe TBI population[136]). Despite these important caveats, PRx monitoring does have several advantages: it is continuous, its impairment relates to poor patient prognosis, and it shows characteristic relationships with other monitored variables such as CPP[80].

Combination monitoring

A potential contributor to the lack of progress in evidence based treatments after TBI is that in clinical trials, physiologic insults are usually viewed in isolation. However, in the complex case of a severely injured TBI patient, a particular physiological impairment is normally viewed in a broader context. For the example of ICP, a value of 20 mm Hg in a patient after craniectomy with impaired cerebral autoregulation, oxygenation and cerebral metabolism should be interpreted differently to a value of 20 mm Hg in a patient with no current ICP directed therapies, and preserved cerebral autoregulation, oxygenation and metabolism. Although the rationale underpinning such a personalised approach is straight-forward, the multiple facets that could or should be considered make the implementation of a truly personalised therapy after TBI difficult.

Focusing on CPP, ICP and PRx, we found that the majority of insults occurred independently. This was particularly so for ICP and PRx and highlights the fact that although the ICP signal is used in the calculation of PRx, it is measuring a different aspect of physiology. Furthermore, the distinction between combined variable insults, and single variable insults is important. The odds of mortality or unfavourable outcome are higher if an ICP or CPP insult was associated with impaired PRx, compared to preserved PRx. These results are supported by recent studies utilising the Brain IT database (minute-by-minute data) that found that if estimated cerebral autoregulation was intact (using a lower frequency analogue of PRx), ICP and CPP insults had less of an effect on patient outcome[137,165].

Limitations

In the current investigation, we estimate the prevalence of intracranial hypertension, low CPP, and deranged autoregulation in a single centre severe TBI cohort. As such, the denominator for prevalence estimate is the number of TBI patients receiving ICP monitoring and having their ICP and ABP signals recorded, which in turn depends on the local clinicians decision on whether ICP monitoring is warranted and whether the research team was available to connect the patient to the computerised monitoring system. This latter point could bias the database against those patients with more short periods with an ICP monitor in-situ. This in turn could lead to either underestimation (if the unrecorded short monitoring periods had more extreme physiology than average) or overestimation (if the unrecorded short monitoring periods had more stable physiology than average) of secondary insults.

An extensive description of admission injury severity (such as pupil reactivity, pre-hospital hypotension or hypoxia) patient treatment (therapeutic intensity level) is not available for this cohort and therefore some confounding could remain unaccounted for. In addition, due to the nature of clinical monitoring, interruptions in the data stream are inevitable for example due to transfer of the patient to scanner or operating theatre. In the majority of this cohort (prior to 2015), the ABP sensor was calibrated to zero at the

level of the right atrium, while after 2015 this was changed to the level of the external acoustic meatus to align with national guidelines[166]. Thus a single ABP will vary ~10 mm Hg depending on where the transducer is zeroed (zeroed at the ear reads ~10 mm Hg lower than at the heart). This could also have contributed to the relatively low number of hours spent with a CPP below 60 mm Hg in this cohort.

Conclusion

ICP and autoregulation insults are common (76% and 92% respectively) after TBI and often occur independently. Concurrent ICP, CPP and PRx insults portend worse prognosis than when a single variable is deranged. Together these data point to the potential benefit of integrating intracranial monitoring modalities at the bedside after severe TBI.

4.2 Long-term changes in patient management, intracranial physiology and mortality

4.2.1 Introduction

Because the management of severe TBI in the acute phase is focused on reducing further injury from insults such as raised ICP or impaired CPP[14], ICP monitoring has become an established standard of care in the management of TBI[78]. Through the pioneering work of Janny, Lundberg and Jennett[167–169] in the middle of the 20th century, clinical ICP monitoring was promoted as a method to optimize the management after TBI. At Addenbrooke's Hospital (Cambridge, UK). continuous intracranial monitoring (including ICP) was introduced in 1991 and thus has been running for over 25 years.

Despite a paucity of positive randomized trials, the management of severe TBI has evolved significantly over the last 50 years. While the first neurosciences intensive care units were opened in in 1932 in Johns Hopkins Hospital (USA) and in the National Hospital for Nervous Diseases (UK) in 1932 and 1954 respectively it was not until the 1980's and 1990's that most large academic institutions were equipped with intensive care units to treat TBI patients. In the UK, recognition of the importance of preventing cerebral hypoxia and hypotension led to several significant changes in TBI management: a transfer of care for TBI patients from the neurosurgical ward to a specialist neurosciences intensive care unit; a focus on ICP and CPP through a dedicated CPP/ICP management algorithm[170]; multimodal brain monitoring; and establishment of national major trauma units to facilitate rapid access to specialized care.

The primary aim of this study was to describe the time related changes of intracranial physiology (as measured by ICP, CPP, and PRx over the past 25-year period in a single academic institution in relation to incremental changes in management strategies.

4.2.2 Methods

Patients

The data in this study was gathered during a retrospective analysis of data collected prospectively from 1146 head-injured patients admitted to the Addenbrooke's Hospital Neurocritical Care Unit between 1991 and 2017. TBI patients with a clinical need for intracranial pressure monitoring and computerized signal recordings were included for analysis. The computerized data storage protocol was reviewed and approved by the local ethics committee of Addenbrooke's Hospital, Cambridge University and the neuro critical care unit User's Group. The study was approved by the institutional ethics committee (30 REC 97/291).

Inclusion criteria were: TBI; invasive monitoring of ICP and ABP for at least 12 hours, admission Glasgow Coma Scale (GCS) and mortality data available. Of the 1146 TBI patients with monitoring data, 1110 patients were included for subsequent analysis. While

some patients in the cohort would be categorized into the moderate TBI group on basis of initial GCS, these patients deteriorated and subsequently required invasive intracranial monitoring and therefore were included in the analysis. Patients were managed according to contemporaneous TBI guidelines. Between 1991 and 1993 patients were managed within the Department of Neurosurgery and general Intensive Care Unit if ventilatory or organ support was needed. A dedicated 12 bed Neurocritical Care Unit was opened in 1994 which was later expanded to 21 beds in 2010 followed by transformation to a major trauma unit and further expansion to 23 beds in 2011.

A protocol aimed at keeping ICP < 20 mm Hg and CPP > 70 mm Hg using step-wise medical and surgical management was implemented in 1994. In 2003, modifications to ICP and CPP targets were introduced (reduction of CPP target to CPP > 60 mm Hg) followed by restricting hyperventilation (end-tidal pCO_2 range adjusted from 4-4.5 kPa to 4.5-5 kPa; figure 4.3). Introduction of multimodal monitoring including microdialysis and brain tissue oxygenation ($P_{BT}O_2$) occurred in 2002 and 2004 respectively. Assessment of the PRx was a part of multimodal monitoring since 1996, however, it was included in clinical assessment (to assist with prognostication) of TBI in 1999. Furthermore, since 2012, autoregulation based CPP targets have been available to try to optimize management as a secondary parameter at the clinicians discretion. In 2015, blood pressure zeroing was changed from the level of the right atrium to the level of foramen of Monro.

All patients were sedated, intubated, and ventilated. The step-wise ICP management included positioning and head elevation, prevention of hypotension and hypoxia and maintenance of end-tidal pCO_2 levels, sedation, muscle paralysis, ventriculostomy, osmotic agents, induced hypothermia, barbiturate coma and decompressive craniectomy. CPP was maintained at target levels using intravenous fluids, vasopressors and inotropes. Tight glucose management was achieved with insulin sliding scale, with target blood glucose levels of between 6 and 8 mmol/L. Seizure management was achieved using phenytoin and levetiracetam as appropriate. Initial Glasgow Coma Scale was obtained for each patient pre sedation. Patients without point breakdown of GCS were included as data for patients before electronic medical records frequently had only total GCS score. Mortality was assessed at 6-months post injury.

Data acquisition

ICP was monitored with an intraparenchymal micro-sensor inserted into the frontal cortex (Codman ICP MicroSensor, Codman & Shurtleff, Raynham, MA) and arterial blood pressure was monitored in the radial or femoral artery (Baxter Healthcare CA, USA; Sidcup, UK) with a zero calibration at the level of the right atrium (1992-2015) and at the foramen of Monro (2015-2017). Between 1992 and 1996 data trends (one-minute time averages) were collected with non-propriety software developed in-house. From 1996-2002 data were sampled at 100 Hz with proprietary data acquisition software (ICM) and one-minute trends were stored. From 2002 -2017 data were collected using ICM+©,

(Cambridge Enterprise, Cambridge, UK-`http://www.neurosurg.cam.ac.uk/icmplus`). PRx was able to be calculated from 1996 onwards. PRx was calculated as the Pearson correlation of 30 consecutive 10-second average values of ABP and ICP. CPP was calculated as ABP- ICP. A 10-second average was used to reduce the influence of respiratory and pulse waveforms. A 300-second moving window was used to generate continuous PRx values.

For each patient, the mean values of ICP, CPP, and PRx were calculated for the duration of monitoring. Indicators of secondary insult were obtained using the percentage time with ICP above 20 mm Hg, percentage time with CPP below 60 mm Hg, and percentage time PRx > 0.25. Plateau waves were identified as an increase in ICP above 40 mm Hg for between 5 and 60 minutes. Severe refractory intracranial hypertension was defined here as an increase in ICP over 40 mm Hg for at least 1 hour.

Statistical analyses

Overall time trends in physiologic variables were investigated graphically by fitting a generalized additive model to the mean physiological variables vs date-time of monitoring. Means, counts, and proportions across 5-year epochs (from 1992-2017) were analysed with a one-way ANOVA, negative binomial regression and the chi-squared test respectively. Holms method was used to adjust for multiple comparisons. All data analysis was performed using the R language for statistical computing[154] with the following packages: 'MASS', 'dplyr', 'ggplot'[149,150,171].

4.2.3 Results

Summary data are shown in table 4.3. 1110 patients were included in the current analysis with a mean age of 37.91. 867 were male and the majority 775 were severely injured on initial GCS assessment. The remainder had a secondary neurological deterioration. The mean duration of monitoring was 114.34 (sd 102.5) hours and 247 (22.25%) died. Figure 4.3 highlights important changes to the intensive care management over the past 25 years.

Table 4.3: Patient demographics; long-term monitoring trends after TBI

	Overall
n	1110
Age [years] (mean (sd))	37.91 (17.23)
Sex = male (%)	867 (78.1)
GCS <= 8 (%)	
FALSE	274 (24.7)
TRUE	775 (69.8)
NA	61 (5.5)
Decompressive craniectomy (%)	
FALSE	469 (42.3)
TRUE	190 (17.1)
NA	451 (40.6)
ICP [mm Hg] (mean (sd))	15.95 (9.34)
CPP [mm Hg] (mean (sd))	76.84 (11.73)
PRx [a.u.] (mean (sd))	0.07 (0.17)
Plateau wave presence = yes (%)	383 (34.5)
Mean number of plateau waves (mean (sd))	5.32 (7.76)
Severe refractory intracranial hypertension presence = yes (%)	94 (8.5)
Mortality [%] = dead (%)	247 (22.3)

ICP intracranial pressure; *CPP* cerebral perfusion pressure; *PRx* pressure reactivity index.
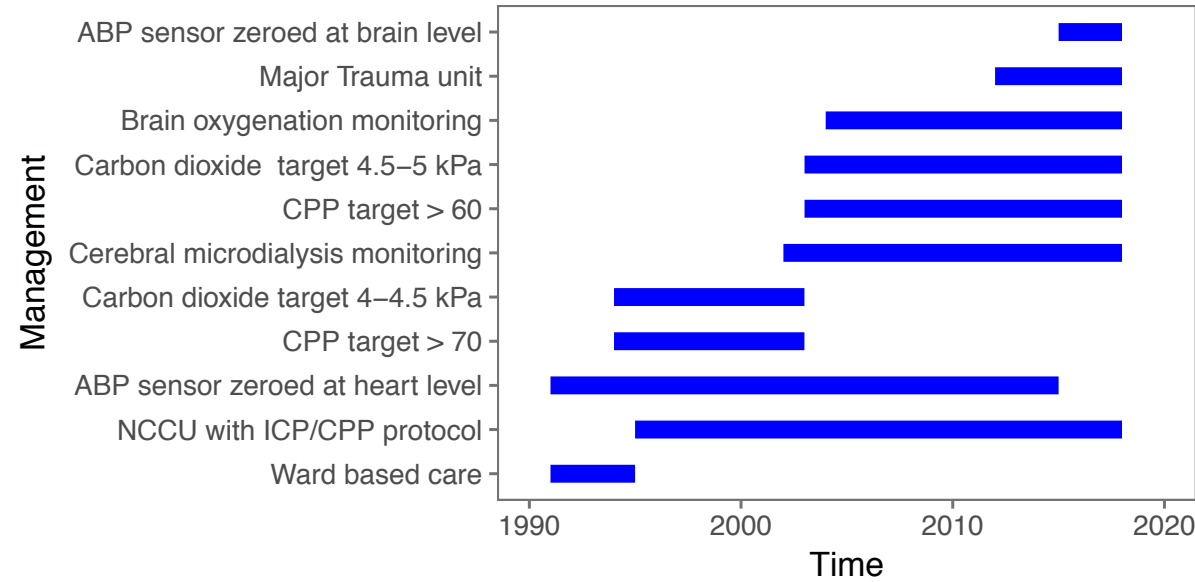
Figure 4.3: **Severe TBI management at Addenbrooke's Hospital over 25 years of ICP monitoring (n=1110).** Over the past 25 years, there have been several changes in the way severe TBI patients have been managed. Before 1994 patients were managed in a neurosurgical annex whereas after 1994 the specialist neurocritical care was opened and a specific ICP/CPP protocol was instituted. Modifications to monitoring parameter targets, and the addition of further neuromonitoring modalities have also occurred. *ABP* arterial blood pressure; *CPP* cerebral perfusion pressure; *ICP* intracranial pressure; *NCCU* neurocritical care unit.*
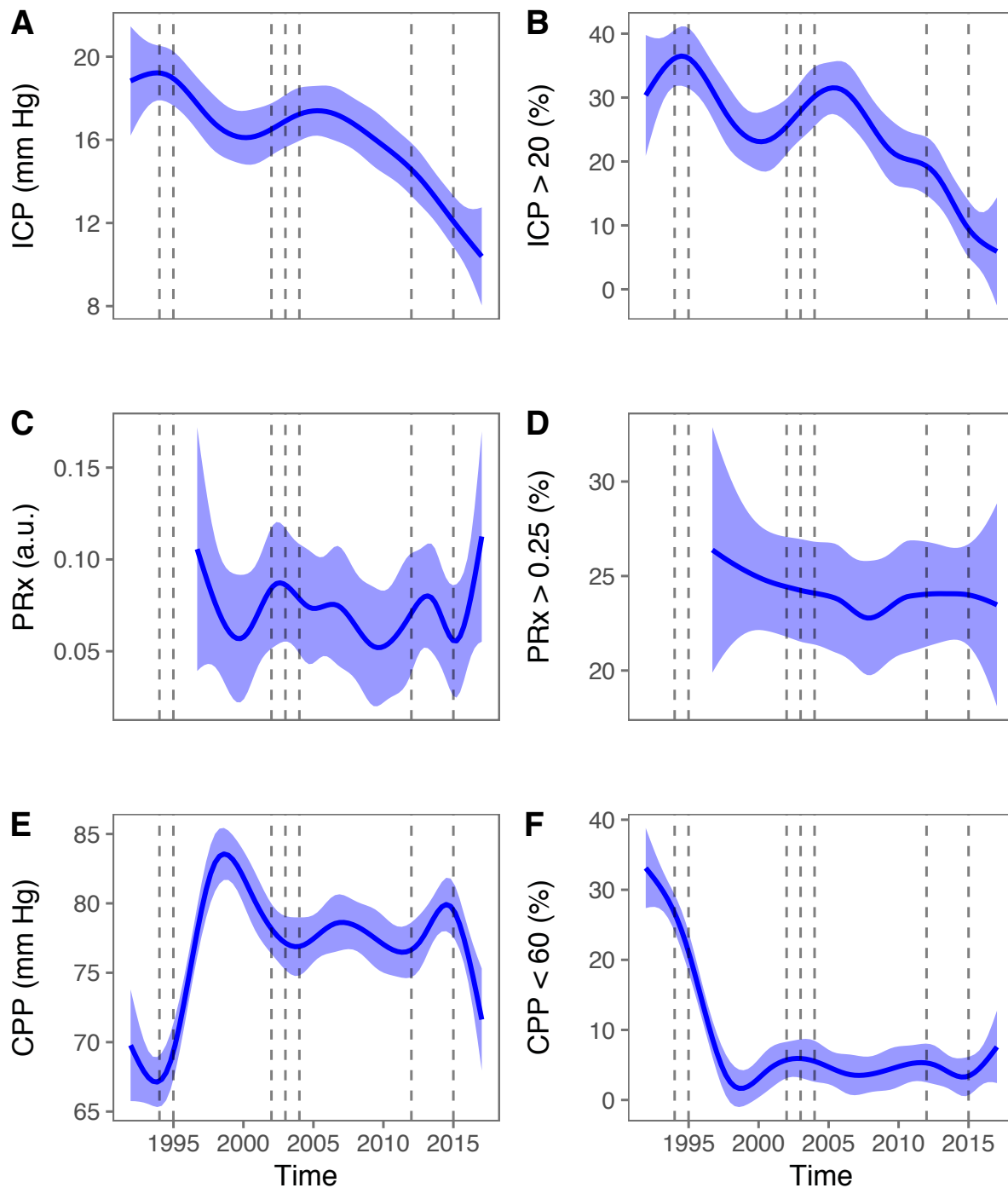
Figure 4.4: **Changes in TBI neuromonitoring variables over 25 years- ICP (top), PRx (middle) and CPP (bottom) (n=1110; generalised additive model).** ICP decreases from just below 20 mm Hg to below 12 mm Hg while CPP increases shortly after 1995 from below 70 to greater than 80 mm Hg around 2000. PRx remains unchanged throughout the 20 years it has been monitored. Key changes in management are indicated by the dotted lines and refer to (in chronological order: Change from ward to NCCU based care (1994); introduction of brain oxygen and metabolism monitoring, relaxation of CO_2 and CPP targets (2002-2004), designation of major trauma unit (2012); and switch from ABP transducer zero at heart to brain level (2015). *ICP* intracranial pressure; *PRx* pressure reactivity index; *CPP* cerebral perfusion pressure.

When mean values of ICP are plotted against time of injury, a consistent decrease from values around 19 mm Hg to below 12 mm Hg are observed over the 25-year period (figure 4.4, individual data points appendix A, figure A.1). CPP showed a distinct increase from ~70 mm Hg in 1994 to above 80 mm Hg in 2000 followed by a gradual reduction and stabilization over the next 15 years at ~ 75 mm Hg. In the final 2 years, CPP decreased by ~7 mm Hg. PRx remained stable throughout the years of monitoring (1996-2017). Statistical analysis confirmed significant effects of time (stratified into five year epochs) for CPP and ICP (including a decrease in number of plateau waves and incidence of refractory intracranial hypertension) but not PRx (figure 4.5). There was an increase in age of monitored patients over time, however, no change in mortality nor GCS (figure 4.6).
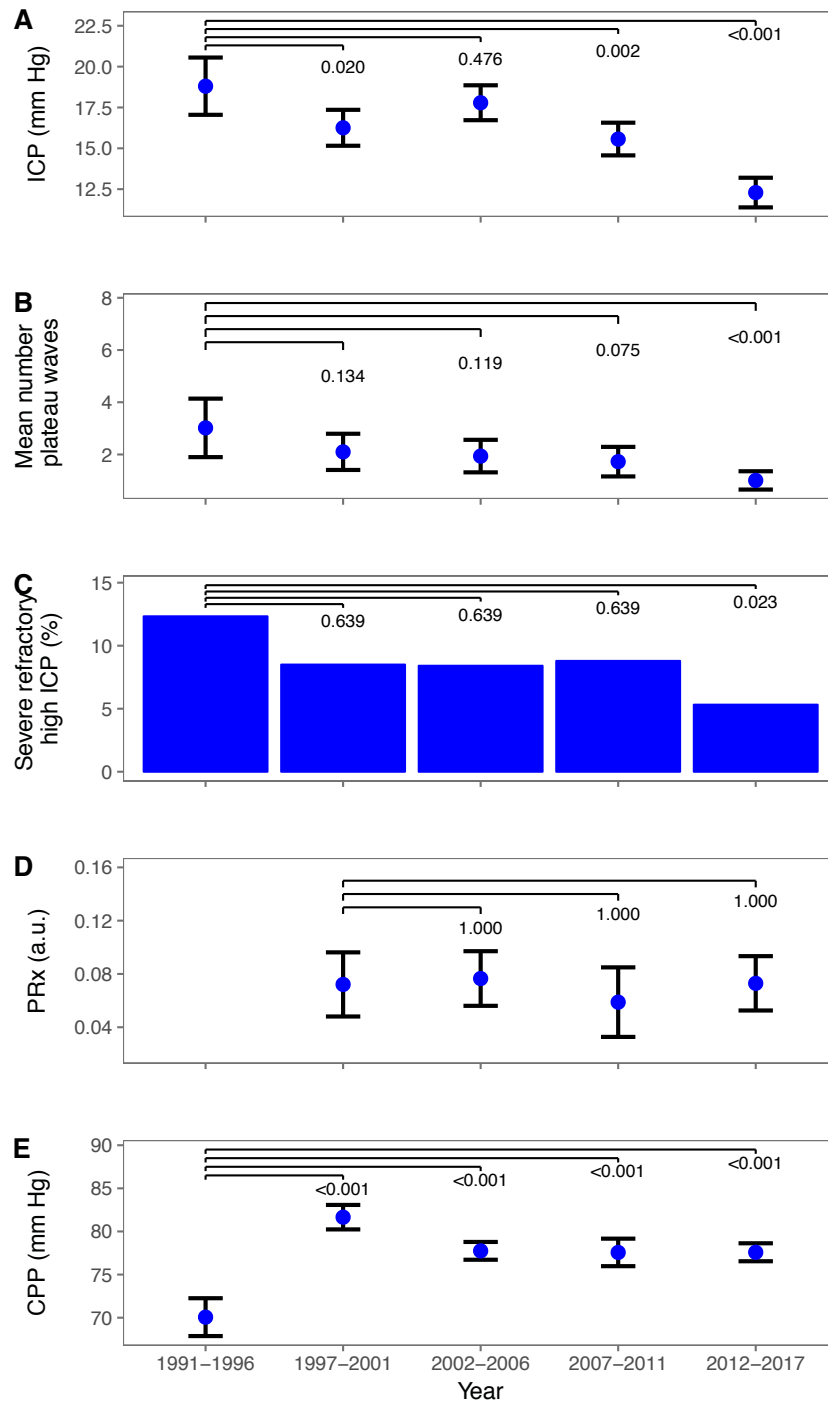
Figure 4.5: **Changes in TBI intracranial monitoring variables over 25 years (error bars represent 95% confidence interval) - ICP, plateau waves, refractory intracranial hypertension, PRx and CPP.** ICP decreases and CPP increases were statistically significant over time. *ICP* intracranial pressure; *PRx* pressure reactivity index; *CPP* cerebral perfusion pressure.
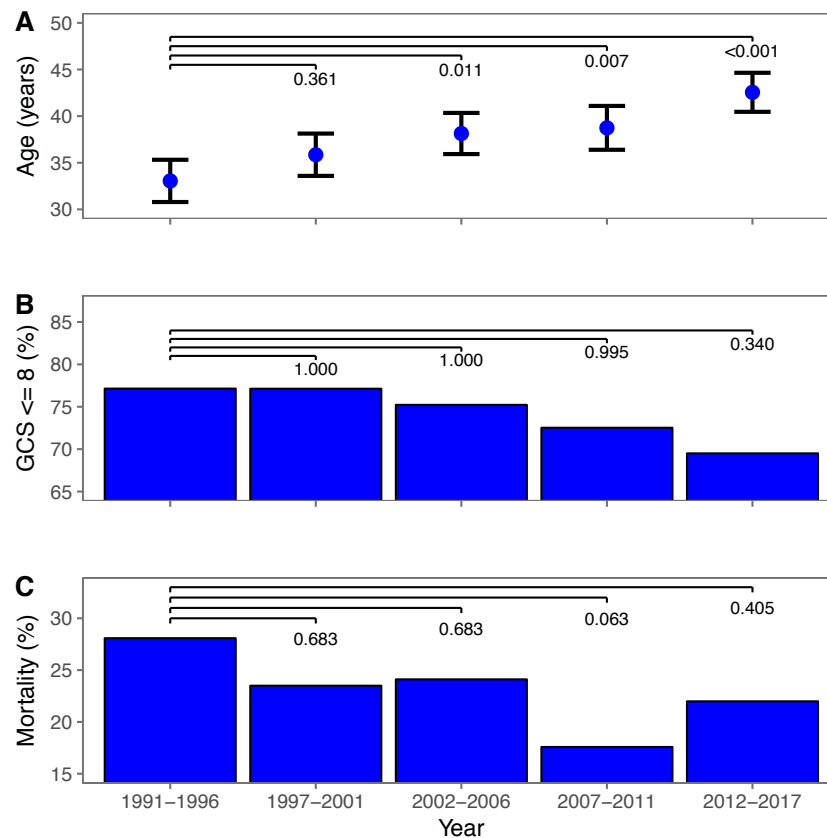
Figure 4.6: **Changes in TBI age, GCS and mortality over 25 years.** The age of patients has significantly increased over time while initial GCS and mortality at 6-months have not significantly altered. *GCS* Glasgow coma scale.

4.2.4 Discussion

Of the multiple incremental changes in TBI management over the past 25 years in this single institution, the introduction of specialized neurocritical care and goal directed therapy had the most pronounced effects on monitored physiology (year 1994, figure 4.4) resulting in increased CPP, decreased ICP, less plateau waves and less time spent outside of ICP or CPP targets. The subsequent introduction of microdialysis, brain tissue oxygenation monitoring or changes in pCO_2 targets and ventilation strategies did not seem to have major immediate effects on ICP, CPP or PRx. Despite an increasing age of the monitored cohort, the mortality has remained low (~22%).

Decreasing mean ICP

The mean ICP decreased over the 25-year period by 8 mm Hg and the percentage of time with ICP over 20 mm Hg also decreased from a mean value of > 30% of monitoring time to < 10%. Because increased ICP is related cerebral blood flow and metabolism[157,172], effective treatment of raised ICP is a prime directive of neurocritical care after TBI[173]. However, defining a precise ICP that warrants treatment is difficult; it is likely the threshold for a damaging ICP will depend on how long the ICP is raised, and whether other cerebral

physiologic markers are also impaired[137,138]. Notwithstanding, the threshold ICP used in this centre was 20 mm Hg for escalating treatment.

The decrease seen in ICP over the years could indicate an increase in frequency in treatments, an increase in efficacy of treatments or perhaps a decrease in the 'baseline' ICP of the monitored cohort. Unfortunately, due to the retrospective nature of the data we do not have exact data on the specific treatments and their timings in each patient. Despite the lack of positive trials on ICP lowering interventions that could be responsible for the results (other than the recent RESCUEicp trial for decompressive craniectomy[161]), the management of TBI has undoubtedly evolved in most neurotrauma centres, including Addenbrooke's Hospital. Such changes have included preference of hypertonic saline over mannitol; use of multimodal monitoring including better access to EEG allowing for more individualized treatment in difficult cases (including seizure management, glucose supplementation, etc.), more rapid access to imaging and identification and treatment of space occupying lesions and potentially increasing use of decompressive craniectomy. Furthermore, with an aging population the age distribution has shifted, albeit modestly, to older patients being admitted, potentially contributing to the lower ICP.

Increasing CPP

The increase in CPP between 1994-1999 is particularly striking and is an example of how the introduction of a management protocol can directly affect patient physiology. CPP oriented therapy developed from the works of Rosner who proposed that maintaining CPP at slightly higher values may decrease the stimulus for vasodilatory ICP waves and thus lead to a more stable ICP[139,174]. Against this background it is interesting to note that the average number of plateau waves per patient decreased after the introduction of CPP oriented therapy (figure 4.4). It became apparent several years after the promotion of CPP oriented therapy, that maintaining high levels of CPP, although effective in preventing secondary insults as measured by jugular bulb oxygen saturation, had no significant effect on neurological outcome possibly due to acute lung injury related to the use of vasopressors and fluids required to maintain an increased CPP[140]. Subsequently most institutions, including Addenbrooke's Hospital, and the Brain Trauma Foundation[175] changed their guidelines to reflect these findings. The decrease of CPP threshold to CPP > 60 mm Hg can be again seen in the time trends in figure 4.4.

Finally, a 7 mm Hg dip in CPP seen after 2015 can be explained by a change in practice, whereby the position of the zero level for the ABP transducer was changed from the level of the right atrium to the level of the foramen of Monro (figure 4.4) to give a clearer indication of the perfusion pressure at the level of the brain[166]. While this does not represent a change in management, it is an example of how systemic changes in practice can effect physiological parameters and needs to be considered during data analysis.

Unchanged pressure reactivity

Pressure reactivity in this single centre cohort did not change over time (figure 4.4). Secondary indices such as PRx derived from continuous monitoring of ICP and ABP can be useful for monitoring various aspects of physiology. PRx has been proposed as a measure of cerebral autoregulation and has the pragmatic advantage over other more direct methods, in that it can be calculated continuously over time[176]. PRx has been demonstrated to related to patient outcome after TBI (worse autoregulation, worse outcome), has been validated in experimental models against gold-standard static autoregulation analysis and has been shown to correspond with the PET based static rate of regulation in adult TBI patients[79,136,177].

Although we have the ability to easily monitor cerebral autoregulation, our ability to improve it is at present limited. Despite early promise of some drugs such as statins[178], there are currently none in use for improving autoregulation. In addition, autoregulation can be affected by many physiological and treatment factors including, CO_2, red blood cell transfusion and body temperature[49,162,163]. Altering physiological conditions has been proposed as a method to improve overall autoregulation and in this light, the concept of CPPoptimal may prove useful[80,81,179–181]. With this method, the CPP at which autoregulation is the most efficient is actively targeted through the careful titration of vasopressors. Despite conceptual promise, its use in clinical practice has been limited[182] due to the lack of prospective clinical studies demonstrating either its safety, or its efficacy. Therefore, the finding that cerebral autoregulation as well as time spent with impaired autoregulation has not changed has not changed over the last 25 years is not surprising.

Nevertheless, as cerebral autoregulation is intrinsically linked to CPP and hence ICP, one could argue that incremental changes in either of these parameters, as well as good neurocritical care with adequate ventilatory support and maintained systemic homeostasis should have exerted beneficial effect on PRx. The obtained results, together with the confirmed independent association with outcome, suggest there is still room for developing interventions targeting cerebral autoregulation

Admission patient characteristics and mortality

Despite the increasing age and steady initial GCS over the 25 years, mortality in the analyzed cohort did not significantly change (figure 4.6). While this is likely contributed to by the sustained improvement in ICP, and better control of CPP, it should be appreciated that patient outcome and in particular mortality are influenced by not only ICP, but also factors not assessed in this study. These factors include the severity of extracranial injuries, co-morbidities, the severity of the primary insult, involvement of critical structures such as the brain stem, as well as patient factors and wishes with respect to withdrawal of care. Indeed, the importance of ICP monitoring after head injury has been recently challenged with the publication of the BEST TRIP trial[158]. It has not been our institutional policy, however, to abandon ICP monitoring. Rather ICP is used in combination with multimodal

monitoring in a interdisciplinary effort (neurointensivists, neurosurgeons, and neurologists) to obtain maximal information about the intracranial physiology and guide specialized therapies.

While the limited nature of the current database prevents detailed analysis of outcome trends over time, our institutional outcomes compare favorably with published data where mortality after severe TBI typically exceeds 25-30%[158,160,161,183]. Indeed a review of severe TBI outcomes in the last 150 years Stein et al.[184] demonstrated that while mortality after head injury decreased significantly in the periods between 1970 - 1990 there was no significant improvement in mortality after 1990, which remained static at around 35%. The reasons for the improvements before 1990 are likely related to the introduction of neurocritical care for head injury patients with good haemodynamic and ventilatory management avoiding hypotension and hypoxemia, rapid access to CT scanning and surgery if required[170]. Since 1995, Brain Trauma Foundation Guidelines have been published[185–187] and Major Trauma Networks have been set up[188] in an attempt to unify care after severe TBI. Some reports suggest improved outcomes with increasing adherence to the Brain Trauma Foundation Guidelines[142,189].

In the UK, neurosurgery services have been centralized since 1948 and therefore volumes and guideline adherence are typically high. Previous UK-based studies have demonstrated reducing mortality over time when all patients with TBI were taken into account[190] and good overall performance when confronted with prediction models[191]. Our data does not strictly confirm this improving trend, however, direct comparison is impossible, as only a selected cohort of patients requiring prolonged intracranial monitoring and neurocritical care was selected for this analysis. Nevertheless, our data, as well as similar studies from other units[183] confirm that it has proven difficult to clearly reduce mortality after severe TBI. Potential reasons for a stagnant mortality rate despite an apparent improved neurocritical care and access to neurosurgery include an aging population, better prehospital survival in patients previously dying on the scene, and an increasing frequency of multitrauma or high velocity accidents.

Limitations

Due to the retrospective nature of this study, the collection of detailed patient outcome assessment, and characterization of patient injury severity (pupil reactivity, CT findings, pre-hospital insults etc.) was not possible. Therefore, inferences from patient outcome results must be treated cautiously. However, the main purpose of the study was to document changes in trends in the monitored physiological parameters and as such, the available ICP, CPP and PRx data suffice to address the research question. In addition, information regarding treatment on a patient-by-patient level may aid in the interpretation of this monitoring data. Unfortunately, such data was unavailable in this database.

Conclusions

In over 1100 patients we demonstrate the evolving trends in neurophysiological monitoring over the past 25 years from a single, academic neurocritical care unit. ICP and CPP were responsive to the introduction of an ICP/CPP goal directed therapy while PRx has remained unchanged.

Chapter 5

Clinical associations with ICP, CPP, and cerebral autoregulation after traumatic brain injury

This chapter is based on data presented in the following publications:

- Donnelly, J., Czosnyka, M., Sudhan, N., Varsos, G.V., Nasr, N., Jalloh, I., Liu, X., Dias, C., Sekhon, M.S., Carpenter, K.L. and Menon, D.K., 2015. Increased blood glucose is related to disturbed cerebrovascular pressure reactivity after traumatic brain injury. Neurocritical care, 22(1), pp.20-25.

- Donnelly, J.*, Young A.*, Smielewski, P.,Czosnyka, M. 2017. Early imaging indicators of increased ICP after paediatric traumatic brain injury. Acta Neurochirurgica. Accepted article.

5.1 Increased blood glucose is related to disturbed PRx after TBI

5.1.1 Introduction

Increased ICP, decreased CPP and impaired PRx have all been associated with poor outcome after TBI (chapter 4) and although impairments of each of these monitored variables are to some degree interdependent, in many cases impairments occur independently (figure 4.1). This highlights the need to search for other influences to monitored intracranial physiology after TBI. One potential influence is the increased blood glucose triggered by the release of catecholamines after TBI[14,192,193]. The increase in blood glucose has been shown to correlate with poorer outcomes following head injury[194] and has lead to a focus on tight glycaemic control protocols[195] on the basis that elevated glucose is a potentially modifiable 'secondary insult,' much like hypotension, hypoxia, and intracranial hypertension.

Mechanisms linking elevated blood glucose to poorer outcomes remain obscure. It has been postulated that increased glucose leads to a hyperglycolytic state, which, if combined with cerebral ischaemia, leads to an increase in cerebral anaerobic metabolism[196,197]. Conversely, another study indicated that increased blood glucose may in fact improve cerebral metabolism[198]. An alternative, and as yet unexplored mechanism, is that increased blood glucose may impair intracranial physiology such as ICP, CPP or cerebral autoregulation.

The aim of this study was to determine if increased blood glucose after TBI has any relationship with ICP, CPP or PRx. We hypothesized that hyperglycemia would be associated with impaired pressure reactivity.

5.1.2 Methods

Patients and methods

The data in this study was gathered during a retrospective analysis of data collected prospectively from 83 head-injured patients admitted to the Addenbrooke's Hospital Neurocritical Care Unit between January 2010 and December 2012. TBI patients with a clinical need for intracranial pressure monitoring were included for analysis. The study was approved by the institutional ethics committee (30 REC 97/291). Inclusion criteria were: traumatic brain injury as diagnosis on admission; invasive monitoring of intracranial pressure and arterial blood pressure; at least 12 hours of monitoring with a coincident blood test. Intracranial monitoring data in the 2 hours before and 2 hours after arterial blood sampling were used.

Patients were managed according to current traumatic brain injury guidelines (based on[14]). Patients were sedated, intubated, ventilated and paralysed. Interventions were aimed at keeping ICP < 20 mm Hg using a stepwise approach of positioning, sedation, muscle paralysis, moderate hyperventilation, ventriculostomy, osmotic agents, and induced

hypothermia. CPP was maintained > 60 - 70 mm Hg using intravenous fluids, vasopressors and inotropes. Glucose management was as per insulin sliding insulin infusion scale, with target blood glucose levels of between 6 and 8 mmol/L. Glasgow outcome scale was assessed at 6 months.

Data acquisition and analyses

ICP was monitored with an intraparenchymal microsensor inserted into the right frontal cortex (Codman ICP MicroSensor, Codman & Shurtleff, Raynham, MA) and arterial blood pressure was monitored in the radial or femoral artery with a zero calibration at the level of the right atrium (Baxter Healthcare CA, USA; Sidcup, UK). End-tidal CO_2 data were collected from the ventilator when available.

Data were sampled at 100 Hz with proprietary data acquisition software ICM+©, (Cambridge Enterprise, Cambridge, UK-`http://www.neurosurg.cam.ac.uk/icmplus`) and stored for subsequent analysis. Data were collected for each day that simultaneous ICP monitoring and arterial blood sampling data were available. PRx was calculated as the Pearson correlation of 30 consecutive 10-second average values of ABP and ICP. For each day, 4 hours of time-averaged cerebrovascular data (CPP, ICP, PRx, end-tidal CO_2) were assessed along with one time-aligned morning arterial blood glucose test taken from the radial or femoral arterial line. Morning arterial glucose values were used as these were routinely collected in every patient and were available on the electronic medical record. Data were collected only for the first 5 days since injury.

Statistical analyses

For the first 5 days since injury, bivariate correlations (Spearman's rho) were calculated between the daily measurement of glucose concentratation and each of the time-aligned monitored variables (ICP, PRx and CPP). Having ascertained a significant univariable relationship between PRx and glucose concentration, the relationship between early glucose and PRx was assessed by calculating the correlation on the first day after injury. To account for the repeated sampling within each patient, a mixed-model was created for estimating PRx as a function of glucose concentration. This model had glucose concentration and potentially relevant covariates (GCS, CPP, ICP, presence of decompressive craniectomy) as fixed effects and patient ID as a random effect. To determine if glucose concentration explained variability in PRx after adjusting for the repeated sampling and important covariates, this full model was compared with a null model that did not include glucose concentration (using a likelihood ratio test). We used the R language and software environment for statistical computation (R Core Team 2015 version 2.12.1)[154] using the following packages: dplyr[149], ggplot2[150], lme4[199]. The significance level was set at 0.05.

5.1.3   Results

Summary details for the 83 patients are shown in table 5.1. The mean age was 41.72, 60 were male and the majority 52 were severely injured on initial GCS assessment. The remainder had a secondary neurological deterioration. 39 ended up with unfavorable outcome (46.99%) and 69 (16.87%) died. Of the 83 patients, there were 256 observations available within the first 5 days since injury.

Table 5.1: Patient demographics; increased blood glucose is related to disturbed cerebrovascular pressure reactivity after TBI

	Overall
n	83
GOS (%)	
D	14 (16.9)
VS	1 (1.2)
SD	24 (28.9)
MD	30 (36.1)
GR	14 (16.9)
Age [years] (mean (sd))	41.72 (18.47)
Sex = male (%)	60 (72.3)
GCS <= 8 = TRUE (%)	52 (62.7)
Decompressive craniectomy = TRUE (%)	20 (24.1)
ICP [mm Hg] (mean (sd))	12.92 (5.76)
CPP [mm Hg] (mean (sd))	76.89 (11.09)
PRx [a.u.] (mean (sd))	0.02 (0.18)
Arterial glucose [mmol/L] (mean (sd))	6.64 (1.13)

  GOS Glasgow outcome score; *D* death; *VS* vegetative state; *SD* severe disability; *MD* moderate disability; *GR* good recovery; *GCS* Glasgow coma scale; *ICP* intracranial pressure; *CPP* cerebral perfusion pressure; *PRx* Pressure reactivity index.
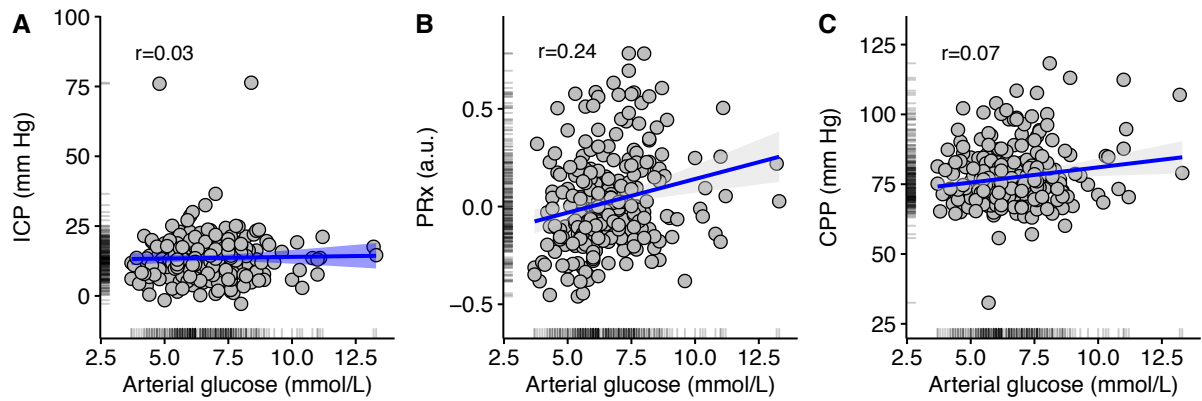
Figure 5.1: **Linear regression (with 95% confidence interval) between morning arterial glucose concentration and ICP (A-left), PRx (B-middle) and CPP (C-right) over first five days of injury.** Arterial glucose concentration was related to PRx but not ICP or CPP over the first 5 days since injury. *ICP* intracranial pressure; *CPP* cerebral perfusion pressure; *PRx* Pressure reactivity index.

Arterial glucose concentration was correlated with time-aligned PRx (Spearman's rho 0.24 (p-value not calculated due to within patient repeated observations); figure 5.1B. When paired glucose concentration and PRx values on the first day from injury were considered, this relationship was stronger (Spearman rho 0.58,0; figure 5.2). Arterial glucose concentration did not show a strong relationship with either CPP or ICP (figure 5.1).

Linear mixed effect models were created to further investigate the relationship between arterial glucose concentration and PRx with accounting for repeated observations within each patient (patient as a random intercept), and for the potential influence on PRx of GCS, CPP, age and presence of decompressive craniectomy (fixed effects). The likelihood ratio test between the full model (fixed effects = glucose, GCS, CPP, age and decompressive craniectomy, random effect = patient ID) and the null model (fixed effects = GCS, CPP, age and decompressive craniectomy only, random effect patient ID) was significant (Chi squared = 9.89, p = 0.002), indicating a significant effect of glucose concentration on PRx after accounting for the given covariates. End-tidal CO_2 may be an important contributor to autoregulation status after TBI, however this data was only available in 57 patients and therefore was not included in the multivariable model. The univariate relationship between mean end-tidal CO_2 and PRx was not strong 0.03 (p=0.85).
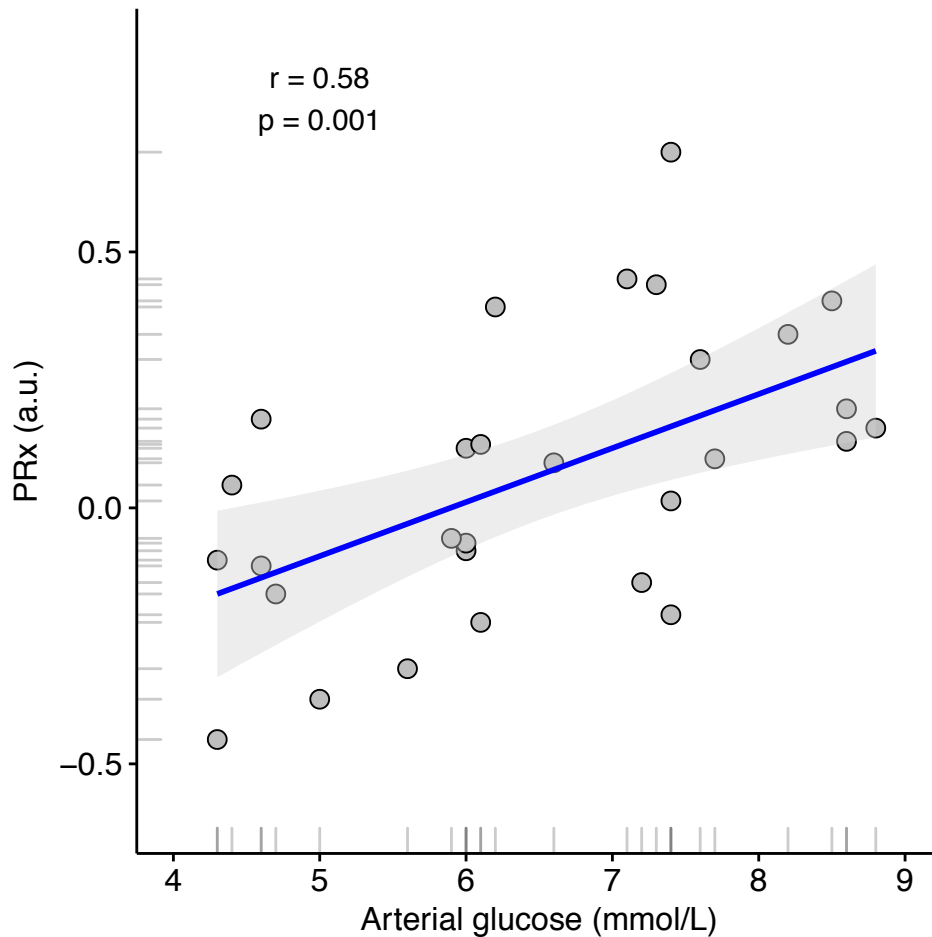
Figure 5.2: **Linear regression (with 95% confidence interval) between morning arterial glucose concentration and ICP (A-left), PRx (B-middle) and CPP (C-right) on day one.** Arterial glucose concentration was related to PRx in the first day after injury. *PRx* pressure reactivity index.

5.1.4 Discussion

The major finding of this study is a significant positive relationship between arterial glucose concentration and cerebral pressure reactivity in TBI patients. There were no relationships between glucose concentration and either ICP or CPP. The relationship was particularly strong on the first day after injury. We propose that hyperglycaemia may lead to poor outcome after TBI, at least in part, due to its hitherto undescribed effect on cerebral pressure reactivity. Two topics warrant further discussion 1) The relation between hyperglycemia and impaired vascular function, and 2) impaired vascular function as a potential causal link between hyperglycaemia and poor outcome after TBI.

Effect of glucose on vascular function

In the current study we found a significant correlation between arterial concentration and PRx in TBI patients (figures 5.1; and 5.2), indicating that arterial glucose may impair cerebrovascular function. Limited data of the effect of glucose on vascular function are

available, particularly in the cerebral circulation. Some experimental data however indicate a glucose-induced impairment of cerebrovascular function. Pre-clinical data from both rats and humans have demonstrated that after administration of glucose, regional cerebral blood flow is decreased[200,201], while experiments in an isolated pial artery preparation observed that elevated glucose concentrations lead to impaired cerebral endothelial function[202].

In addition to impairing the cerebral circulation, elevated blood glucose concentration has been shown to impair vascular function systemically. In non-diabetics, oral glucose loading impairs endothelial function as measured with flow mediated dilation in the upper limb[203] and in healthy humans, oral glucose loading impairs brachial artery myogenic vasoconstriction.[204].Taken together, these experimental data indicate that elevated blood glucose concentration impairs endothelial, and smooth muscle cell responses both in the cerebral and peripheral vasculature. Clearly, further investigation on the link between glucose and pressure reactivity in the TBI population is warranted.

Impaired vascular function as a mediator between hyperglycaemia and outcome after TBI

Although not assessed in the current study due to sample size and sampling frequency, the association between elevated glucose and poor outcome after traumatic brain injury is well established[194,205,206]. However, the physiological significance of this association has been debated. Because hyperglycemia is a common finding in many acute conditions and is related to the initial GCS[194], it is possible that hyperglycaemia is epiphenomenal of a systemic stress response and is a reflection of injury severity. Furthermore, recent evidence purports that mild hyperglycaemia may be in fact be beneficial to cerebral metabolism[207].

Other evidence, however, indicates that after TBI, hyperglycaemia *per se* is harmful. Hyperglycaemia leads to an increased anaerobic metabolism and acidosis in the brain[196,208] which in turn can contribute to neuronal dysfunction and brain oedema. Even mild increases in arterial blood glucose are associated with cerebral anaerobic metabolism as assessed by jugular oximetry[209]. In addition, elevated brain glucose concentrations (greater than 5 mM) have been associated with increased concentration of the excitotoxic brain glutamate, a substance known for its excitotoxic properties[210].

Our preliminary findings indicate that, in addition to these detrimental metabolic effects, hyperglycaemia may impair vascular function. Some support for such a link in disease models can be found in the stroke biology literature. In a rat model, Kawai and colleagues demonstrated that a higher blood glucose leads to a greater size of infarction[211,212] whilst in humans, diffusion-weighted MRI in post-stroke patients revealed that increased blood glucose concentration early in the clinical course is associated with an increase in infarction volume[213]. Therefore, evidence indicates that hyperglycaemia is associated with a greater ischaemic burden, which, combined with our data, leads us to speculate that the adverse effects of hyperglycaemia on outcome in TBI could be mediated, in part, by impaired cerebrovascular function.

Limitations

The current study has several important limitations. First, the small number of patients (83) raises the possibility of type 1 statistical error, especially given the exploratory nature of this investigation. However, the relationship remained significant after multivariable adjustment (including aspects of injury severity and other monitored physiology), and has some plausible physiological underpinnings (discus above). These results should be investigated in a larger cohort. Second, glucose concentration data were collected only daily. Because of this low density of data points, a detailed analysis of the time-course of the glucose and PRx dynamics within patients was not performed. Third, glucose concentration was assessed systemically (arterial blood) rather than locally (cerebral microdialysis). Brain tissue glucose concentration could yield additional insight into the relationship between glucose and cerebral autoregulation, however the focus of this study was to assess the influence of the prevailing glucose concentration presented to the whole brain, rather than the localised microdialysis glucose concentration in peri-lesional brain tissue. Finally, although we speculate that a glucose-mediated impairment of cerebral autoregulation may explain in part, worse outcomes in patients with hyperglycaemia, we have not assessed the effect of glucose on outcome in the current study. Such an analysis would likely need a high density of glucose measurements, or glucose concentrations very early after injury.

Conclusion

We have demonstrated that mild elevation of arterial glucose concentration impairs cerebrovascular pressure reactivity but does not affect ICP or CPP, and propose that this effect may be a mechanistic link between elevated glucose concentration and poor outcome in TBI.

5.2 Association between early imaging and intracranial pressure after paediatric traumatic brain injury; an exploratory analysis

5.2.1 Introduction

Traumatic brain injury remains a major public health problem, particularly in children, where it is one of the leading causes of death and disability[214]. While the early management phase of severe TBI aims primarily to reduce neurological damage by limiting secondary insults to the brain, another important component is to appropriately select patients that require further intensive neuromonitoring[215].

While monitoring intracranial pressure is a standard of care in adult severe TBI, it could be argued that the same should be true for the paediatric population; those that die or have unfavourable outcome tend to have higher ICP than those who survive or have a good outcome[137,179–181,216,217]. However, deciding which patients are most at risk of developing high ICP and therefore may derive benefit from invasive ICP monitoring is difficult[218]. Current guidelines in adults suggest that ICP monitoring should be considered when GCS is less than or equal to 8 and the initial CT scan is abnormal or if other adverse prognostic factors are present such as age over 40, abnormal motor posturing, or hypotension[134]. Early imaging can help identify severely injured patients that may be high risk of poor outcome[219]. The cerebral CT scan can show intracranial pathophysiology (traumatic subarachnoid blood (SAH), masses, or mid-line shift) or indicate the consequence of raised ICP (size of basal cisterns). How these early imaging features subsequently influence the continuously monitored ICP on the paediatric intensive care unit has not been investigated.

In this study we describe how early imaging pathology after severe paediatric TBI may be related to ICP in the intensive care unit.

5.2.2 Methods

Patients

The data in this study were collected retrospectively from data records of paediatric severe traumatic brain injury patients admitted to Addenbrooke's Hospital Paediatric Intensive Care Unit (PICU) between October 2002 and December 2015. The data is routinely collected for clinical purposes and guides the management of patients. The analysis of data within this study for the purposes of service evaluation was approved by the Cambridge University Hospital NHS Trust, Audit and Service Evaluation Department (Ref: 2143) and did not require ethical approval or patient consent.

All patients requiring invasive ICP monitoring on the PICU and with a confirmed traumatic brain injury on CT or MRI were included for this analysis. Patients were managed according to local trust guidelines based on the concurrent international evidence

TBI guidelines[220]. Interventions were aimed at keeping ICP < 20 mm Hg using a tiered treatment protocol of positioning, sedation, muscle paralysis, moderate hyperventilation, ventriculostomy, osmotic agents, and induced hypothermia. Pre-hospital data (first recorded pupil reactivity and motor score) were obtained from the ambulance records which are included as part of the patient's medical notes. Admission CT scans were independently reviewed for the width of the basal cisterns (mm), and the presence of subarachnoid blood, petechial haemorrhage, or mid-line shift.

Data Acquisition and Processing

ICP monitoring was commenced at the nearest possible opportunity after the patient had been transferred to the tertiary setting and was terminated when sedation was lifted and the child either began to waken or when the patient died. The average duration of data collection for the cohort was 5.3 days. ICP was monitored with an intraparenchymal microsensor inserted into the frontal cortex (Codman ICP Micro- Sensor, Codman & Shurtleff, Raynham, MA) and signals were digitized using an A/D converter (DT9801, Data Translation, Marlboro, MA), sampled at a frequency of 100 Hz, and recorded and analysed using a laptop computer with ICM+® software (University of Cambridge, Cambridge Enterprise, Cambridge, UK, `http://www.neurosurg.cam.ac.uk/icmplus`). Artefacts were manually identified after data collection and excluded from further analysis. Mean ICP was calculated over the first 72 hours of monitoring.

Statistical Analysis

Mean ICP was summarized as the medians with associated interquartile range (IQR). Differences in mean ICP between those with, and without the presence of each of the imaging findings were interrogated with the Wilcox test. Spearman's rho was used to assess the correlation between basal cistern width and mean ICP. Significance level was set to 0.05, and all tests were two-tailed and unadjusted for multiple comparisons. All data manipulation and statistical analyses were conducted in the R language and software environment for statistical computation (version 2.12.1)[147] using the dplyr[149], ggplot2[150] packages.

5.2.3 Results

Summary details for the 39 patients are shown in table 5.2. The mean age was 10.58 and 25 were male. 12 had an initial GCS motor score of less than or equal to 4, and 7 had at least 1 unreactive pupil. 15 (38.46%) had focal injury on CT and the remainder diffuse axonal injury. 8 ended up with unfavorable outcome (20.51%) and 7 (17.95%) died. An example of computerised intracranial pressure monitoring in two paediatric TBI patients is shown in figure 5.3.

Table 5.2: Patient demographics; association between early imaging and intracranial pressure after paediatric traumatic brain injury

	Overall
n	39
GOS (%)	
D	7 (17.9)
VS	1 (2.6)
SD	3 (7.7)
MD	13 (33.3)
GR	15 (38.5)
Age [years] (mean (sd))	10.58 (5.33)
Sex = male (%)	25 (64.1)
GCS motor score <=3 = TRUE (%)	12 (30.8)
At least 1 unreactive pupil = TRUE (%)	7 (17.9)
ICP [mm Hg] (mean (sd))	18.85 (14.24)
CPP [mm Hg] (mean (sd))	67.96 (12.60)
PRx [a.u.] (mean (sd))	0.02 (0.29)

GOS Glasgow outcome score; *D* death; *VS* vegetative state; *SD* severe disability; *MD* moderate disability; *GR* good recovery; *GCS* Glasgow coma scale; *ICP* intracranial pressure; *CPP* cerebral perfusion pressure; *PRx* Pressure reactivity index.
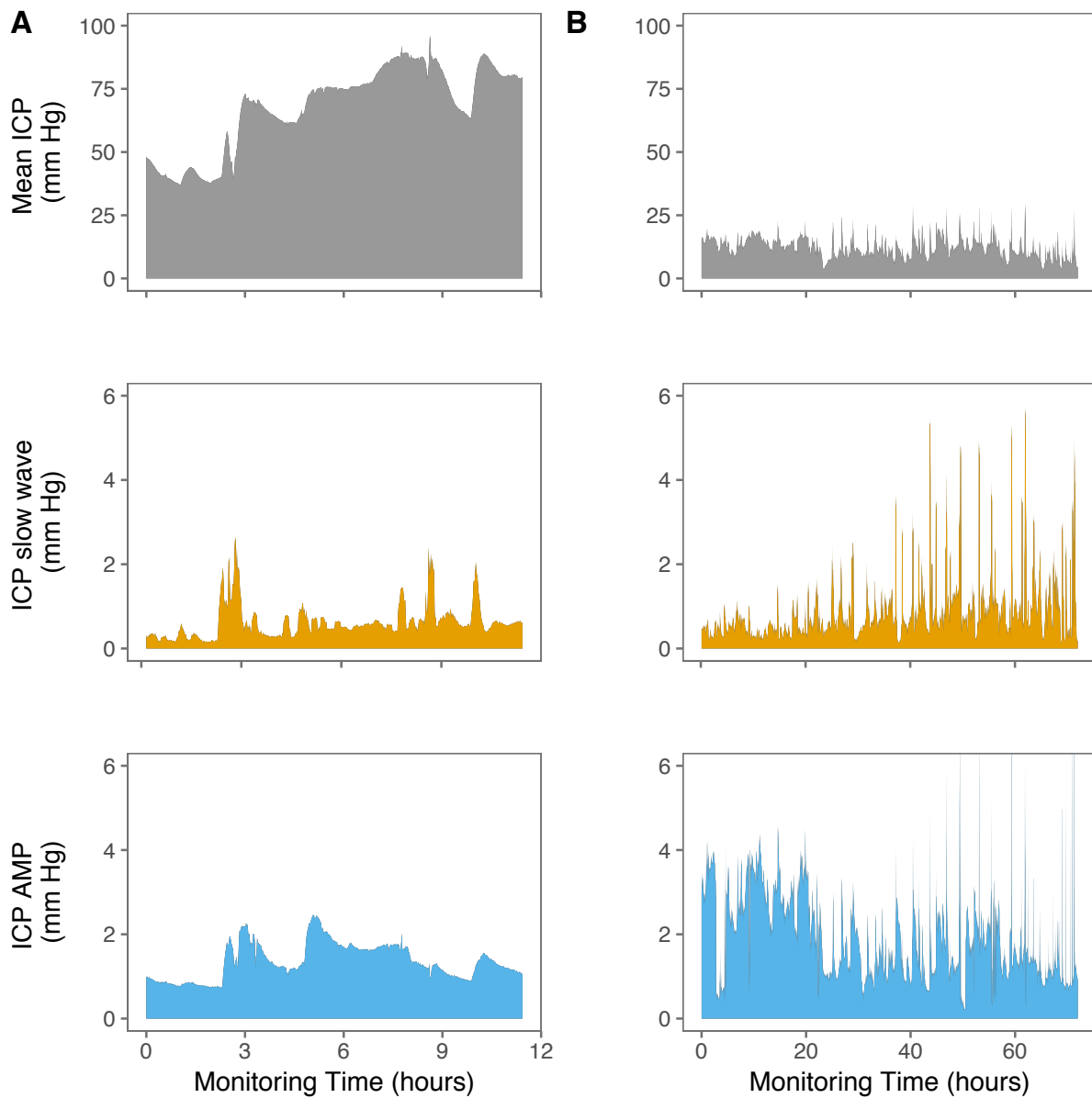
Figure 5.3: **ICP monitoring after severe paediatric TBI.** The left panel depicts the ICP monitoring trends from a 15 year old female who presented with a motor score of 4, and bilaterally reactive pupils. The initial CT scan showed subarachnoid blood and diffuse swelling. The patient went on to have ICP monitoring and developed fatal severe intracranial hypertension. The right panel shows ICP trends from a 3 year old male who similarly presented with a motor score of 4, bilaterally reactive pupils and diffuse swelling on initial CT. The patient however had no subarachnoid blood on initial CT. This patient had low and stable ICP over the subsequent intensive care stay (mean ICP 11 mm Hg) and had a good recovery 6 months after ictus. *ICP AMP* pulse amplitude of ICP; *ICP slow wave* effective slow wave power of ICP.
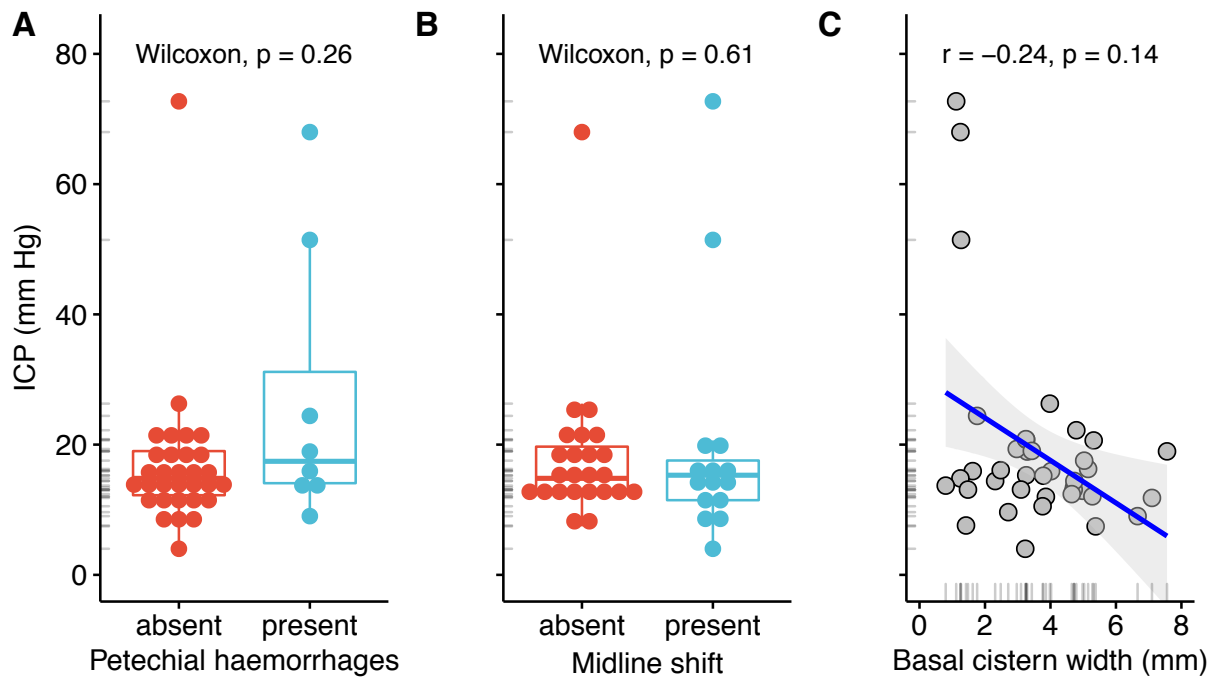
Figure 5.4: **Relationship between ICP during the first three days and features on the initial cerebral CT after paediatric TBI.** The presence of petechial haemorrhages (A- left) or mid-line shift (B- middle) did not relate to the subsequent mean ICP. The width of the basal cisterns was not significantly related to ICP, although the three patients with severe intracranial hypertension (>40 mm Hg) all presented with initial cerebral CT scans demonstrating compressed basal cisterns. *ICP* intracranial pressure.

Patients with traumatic subarachnoid haemorrhage on initial CT subsequently developed higher ICP over the next 3 days of monitoring 20.09 (IQR 16.27) mm Hg vs 14.41 (IQR 4.78) mm Hg, p= 0.01), figure 5.5. The presence of mid-line shift and petechial haemorrhages did not lead to significant differences in subsequent ICP (figure 5.4), whereas those with more compressed basal cisterns showed a tendency to have higher ICP (Spearman rho -0.24, p value 0.14 - figure 5.4). Moreover, of the patients who developed severe intracranial hypertension (mean ICP >40 mm Hg), all three had compressed cisterns on admission.

Although not the primary aim of this exploratory study, ICP was related to mortality with those who died displaying higher median ICP (area under receiver operating curve: 0.82 (95% CI 0.63- 1)).
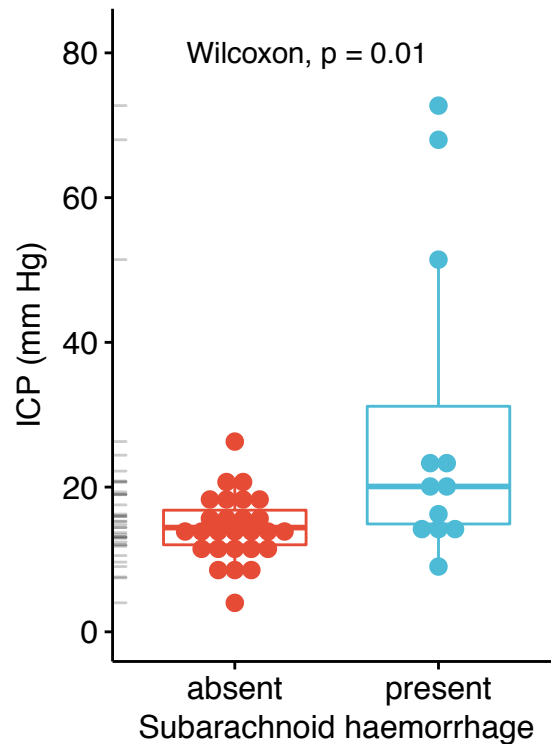
Figure 5.5: **Relationship between ICP during the first 3 days and traumatic subarachnoid haemorrhage on the initial cerebral CT after paediatric TBI.** The presence of subarachnoid haemorrhage was significantly related to higher mean ICP over the first 3 days of monitoring in the intensive care unit. *ICP* intracranial pressure.

5.2.4 Discussion

In this exploratory analysis, we demonstrate that mean ICP in the first three days of intensive care treatment after paediatric TBI was dependent on the presence of subarachnoid haemorrhage on the initial CT scan. We herein discuss possible explanations, implications and caveats.

Explanations

Subarachnoid blood on the initial CT in this paediatric TBI cohort was associated with higher levels of ICP recorded with computerised ICP monitoring. This confirms a previous finding in adult TBI from the Traumatic Coma Data Bank that demonstrated that those with traumatic subarachnoid haemorrhage spent more time with ICP greater than 20 mm Hg as assessed using end-hour ICP measurements[221]. While aneurysmal SAH has been fairly extensively studied, the implications of traumatic SAH are less well understood. This is despite the fact that subarachnoid haemorrhage after TBI is common (reported at 68% of severe paediatric TBI patients[219], and between 40 and 80% in adult TBI[222–224]), and is an independent predictor of patient outcome[221,222,224,225]. Traumatic subarachnoid haemorrhage could potentially lead to elevated ICP by means of the development of hydrocephalus[226] or, if vasospasm occurs, cerebral ischaemia and oedema[227]. Supporting

the latter, an adult adult TBI study found those with a higher volume of subarachnoid blood on initial CT scan developed worse cerebral oedema on serial CT examination[228]. The failure of finding a significant relationship between other imaging findings (mid-line shift, basal cistern compression or petechial haemorrhages) could indicate that these factors, which are known have an effect on prognosis[229]), exert their effect on outcome via ICP independent pathways, or alternatively it could be that factors such as midline shift and basal cistern compression are dynamic and therefore associate with instantaneous ICP but not subsequent longer term (i.e. 3 day) ICP. Finally, relationships may be too subtle to be appreciated in our current sample size as it is important note that basal cistern compression and midline shift have previously been associated with elevated ICP in a large adult TBI data bank[221].

Implications

Although some factors (dilated pupils, subdural haematoma, basal cisterns compression, optic nerve sheath diameter) have been associated with simultaneous increases in ICP after paediatric TBI[179,230], the effect on ICP control for several days following is unknown. Our finding of an association between initial SAH and subsequent high ICP indicates that this should alert the clinician to potential ICP control difficulties. In addition, given that traumatic SAH is related to ICP and has also been associated with patient outcome[146,222], it represents a potential confounder that should ideally be included as a covariate in studies associating ICP with clinical outcome.

While the width of the basal cisterns was not significantly related to ICP in this cohort, examination of the scatter plot reveals that the patients with the highest levels of ICP all had very small cisterns, and therefore larger sample sizes including more patients with elevated ICP will likely produce a statistically significant relationship. However, an important implication of figure 5.4 is that having compressed basal cisterns on the initial CT scan may be associated with near normal levels of ICP and conversely having relatively open cisterns does not guarantee well-controlled ICP in the following three days.

Caveats

A major limitation of this exploratory analysis is the small dataset (n=39), which increases the risk of both type 1 (falsely positive), or type II (falsely negative) results[117]. This number was chosen as it is the sum total of patients in our current high resolution paediatric monitoring database and highlights the need for replication in larger datasets. Particular caution should be applied with the failure to find a siginificant relationship between midline shift or basal cistern compression and ICP. Further information on any treatments occuring between the initial CT scan and the ICP monitoring (for example, evacuation of haematoma) would aid interpretation of the data. In addition, basal cistern size can be difficult to assess (with no age specific reference range available). Univariable relationships of CT findings with ICP were investigated, despite the fact that in many cases,

CT abnormalities occured together. Larger studies should aim to assess multivariable relationships between CT abnormalities and subsequent ICP.

This study assessed the relationship between the initial cerebral CT scan and the mean ICP that could be temporally dissociated by up to 3 days. Therefore, comparison with other studies that for example relate CT findings with concurrent ICP after TBI should be made with caution[179,230]. Because of the limitations of performing multiple hypothesis tests on a small dataset, the relationship of the initial CT findings with pressure reactivity was not assessed. Given the paucity of severe paediatric TBI ICP monitoring data, national and international data sharing initiatives are perhaps the only feasible avenue for robust hypothesis testing in this field.

Conclusion

In paediatric TBI, patients presenting with subarachnoid blood on the initial CT scan should be deemed as high risk for developing problems with ICP control.

Chapter 6

Intracranial sequelae of raised intracranial pressure

This chapter is based on data presented the following publication:

- Donnelly, J., Czosnyka, M., Harland, S., Varsos, G.V., Cardim, D., Robba, C., Liu, X., Ainslie, P.N. and Smielewski, P., 2017. Cerebral haemodynamics during experimental intracranial hypertension. Journal of Cerebral Blood Flow & Metabolism, 37(2), pp.694-705.

6.1 Cerebral haemodynamics during experimental intracranial hypertension

6.1.1 Introduction

Intracranial hypertension is a final pathophysiologic feature common to many neurological conditions including intracranial hemorrhage, acute shunt blockage in hydrocephalus, or TBI[231], however, the haemodynamic sequelae are incompletely described. Increases in ICP decrease CPP and limit CBF[232], however, this reduction in CBF is compensated to a degree because with sustained decreases in CPP, the brain exhibits active vasodilation in attempt to maintain CBF – cerebral autoregulation[7,9,10]. Recent studies indicate that the CBF response to a decreased CPP caused by decreasing ABP, or increasing ICP have key physiological differences[181,233,234]. In addition, the haemodynamic response to increased ICP is complicated by presence of the "Cushing response" – arterial hypertension, changes in heart rate, and breathing abnormalities[235].The effect this Cushing response has on cerebral haemodynamics remains unclear.

In this study we revisited the question of haemodynamic responses to graded and severe increases in ICP. Utilizing recent advances in mathematical modelling of cerebral haemodynamics, combined with global and local assessment of cerebral perfusion, we aimed to describe cerebrovascular perfusion, critical closing pressure, vascular wall tension during experimental increases in ICP.

6.1.2 Methods

Animals and ethics

These experiments were carried out in 1995 (not collected by thesis author) in accordance with the standards provided by the UK Animals Scientific Procedures act of 1986 under a UK home office license and with permission from the institutional animal care and use committee at Cambridge University. All analyses and interpretation for this project were performed by the thesis author.

Physiological recordings from lumber CSF infusions in 27 NZ White rabbits were retrospectively analysed[236]. General anesthesia was induced using intravenous alphax-alone/alphadalone (Saffan, Pitman-Moore, Uxbridge, UK, 0.2 mL/kg) and maintained using 1-3% halothane at 1.5% in 3:1 nitrous oxide/oxygen. Two weeks prior to the experiment, rabbits had their common carotid artery ligated to ensure that blood flow to the brain was basilar artery dependent.

On the experimental day, anaesthesia was repeated as above. The jugular vein was cannulated and a tracheostomy was performed. ABP was measured in the dorsal aorta after catheter insertion in the femoral artery (GaelTec, Dunvegan, UK). Cerebral blood flow velocity was measured using an 8 MHz Doppler ultrasound probe (PCDop 842, SciMed, Bristol, UK) positioned over the basilar artery (accessed through a 7mm burr-hole at

the bregma as described previously[237]. ICP was monitored using an intraparenchymal microsensor (Codman and Shurtleff, Raynham, MA, USA) inserted through a right frontal burr-hole and a laser Doppler flowmetry probe was placed epidurally through a further right frontal burr-hole (Moor Instruments, Axbridge, Devon, UK). A lumbar laminectomy was performed to allow the positioning of a permanent catheter (sealed with cyanoacrylate after introduction) into the lumbar subarachnoid space to allow controlled infusion of artificial CSF. Rectal temperature was monitored and the animals placed on a padded warming blanket. The rabbits were given an intravenous infusion of pancuronium (pavulon, 0.5 mg/kg/hour) and ventilation was controlled according to carbon dioxide concentrations on periodic arterial blood gas analyses.

Protocol

After a CO_2 reactivity test (data not analysed here) rabbits were rested for 20-minutes before a 10-minute period of baseline recordings, ICP was artificially increased by infusion of Hartmann's solution into the lumbar CSF space. Infusion rates were initially 0.1 mL/min. ICP gradually increased to reach a plateau around 40 mm Hg, thereafter the infusion rate was rapidly increased at rates between 0.2 and 2 ml/min to produce rapid and severe intracranial hypertension. ICP at termination of experiment was typically between 70 and 100 mm Hg. Rabbits were euthanized with thiopental at the conclusion of the test.

Data acquisition and analysis

ABP, ICP, and Fv and expired CO_2 signals were recorded digitally at a sampling frequency of 50 Hz. Data were subsequently analysed off-line using ICM+® software (University of Cambridge, Cambridge Enterprise, Cambridge, UK, `http://www.neurosurg.cam.ac.uk/icmplus`). HR was calculated by estimating the fundamental frequency of ABP spectra in a moving 10 second window. Diastolic and systolic values of blood pressure and flow velocity were calculated by estimating the minima and maxima over a 0.5 second window, shifted each .25 second. Mean values were then calculated over 10 second period. LDF was expressed as a.u. minus the 'biological zero' as measured in the asystolic rabbit at the conclusion of the experiment. Mean values of ABP, ICP, LDF, and Fv were calculated every 10 seconds. Fundamental amplitudes of ICP, ABP, and Fv were calculated using by spectral analysis within the range of the rabbits HR (100-400 bpm). End-tidal CO_2 values were corrected using the arterial PCO_2 concentration from the blood gas analysis to account for any end-tidal to arterial PCO_2 gradients.

Critical closing pressure was calculated using both measured (MAP, HR, CPP) and modelled variables (CVR; Ca - cerebral arterial compliance) as described in[238] and shown below:

$$CrCP = MAP - \frac{CPP}{\sqrt{(CVRi \times Ca \times HR \times 2\pi)^2 + 1}} \qquad (6.1)$$

Where CrCP = critical closing pressure, MAP = arterial blood pressure, CPP = cerebral

perfusion pressure, CVRi = cerebrovascular resistance (invasive, i.e. calculated as CPP divided by mean blood flow velocity), Ca = cerebral arterial compliance, HR = heart rate. Arterial wall tension (WT) was calculated as CrCP- ICP.

Although data across the whole recording period were analysed, three points of interest were identified to allow statistical comparisons of intracranial haemodynamics: baseline before any infusion ("baseline ICP"), during a plateau of ICP immediately prior to the final steep rise in intracranial pressure ("elevated ICP"), and in the period between the final rise in ICP and termination of the experiment ("severe ICP").

To compare cerebral perfusion as measured by LDF and Doppler ultrasound, both LDF and Fv were expressed as a percentage of their value at baseline. For each rabbit, the mean LDF (% of baseline) and Fv (% of baseline) was calculated in 10 mm Hg wide intervals of CPP or ICP. A locally weighted scatter smoothing (LOWESS) function was applied to the grouped mean data of the cohort.

Statistical analyses

The relationship between minute-by-minute values of mean ICP and ICP pulse amplitude was fitted with a generalised additive model allowing for 3 different segments (cubic regression spline smooths). The number of segments (3) was chosen *a priori* to allow for 3 different portions of the ICP, AMP relationship (~flat at low ICP, steep rising segment, and an upper breakpoint). Pairwise comparisons between physiological variables at the different ICP levels were performed using students t-test. Alpha-value was set at 0.05 and no corrections were made for multiple comparisons. All data manipulation and statistical analyses were conducted in the R language and software environment for statistical computation (version 2.12.1)[147].

6.1.3   Results

Monitored variables during a typical CSF infusion experiment are depicted in figure 6.1. ICP gradually increased due incremental increases in the rate of CSF infusion. In this case, cortical perfusion, as indicated by laser Doppler flowmetry showed a monotonic decrease with increasing ICP, whereas global perfusion, as assessed by basilar artery flow velocity, was well maintained until ICP reached values greater than 40 mm Hg. MAP remained stable until ICP increased above 40 mm Hg, at which point it started to increase significantly.

Figure 6.2 shows selected derived haemodynamic variables in the same rabbit during the final segment of the experiment (ICP increasing above 40 mm Hg). As a result of this raised ICP, calculated CrCP increased and eventually reached values equivalent to the diastolic ABP. At this point the diastolic closing margin (diastolic ABP minus CrCP) is equal to zero or negative indicating that the forces acting to close the microvasculature are greater than the forces keeping the vessels open. This coincided with a cessation of diastolic flow velocity. The amplitude of ICP (AMP) increased with increasing mean ICP

with the exception of at very high levels of mean ICP at which point AMP appeared to decrease. This phenomenon of an 'upper break-point' of the amplitude-mean pressure was observed in 5 of the 27 rabbits (figure 6.3).
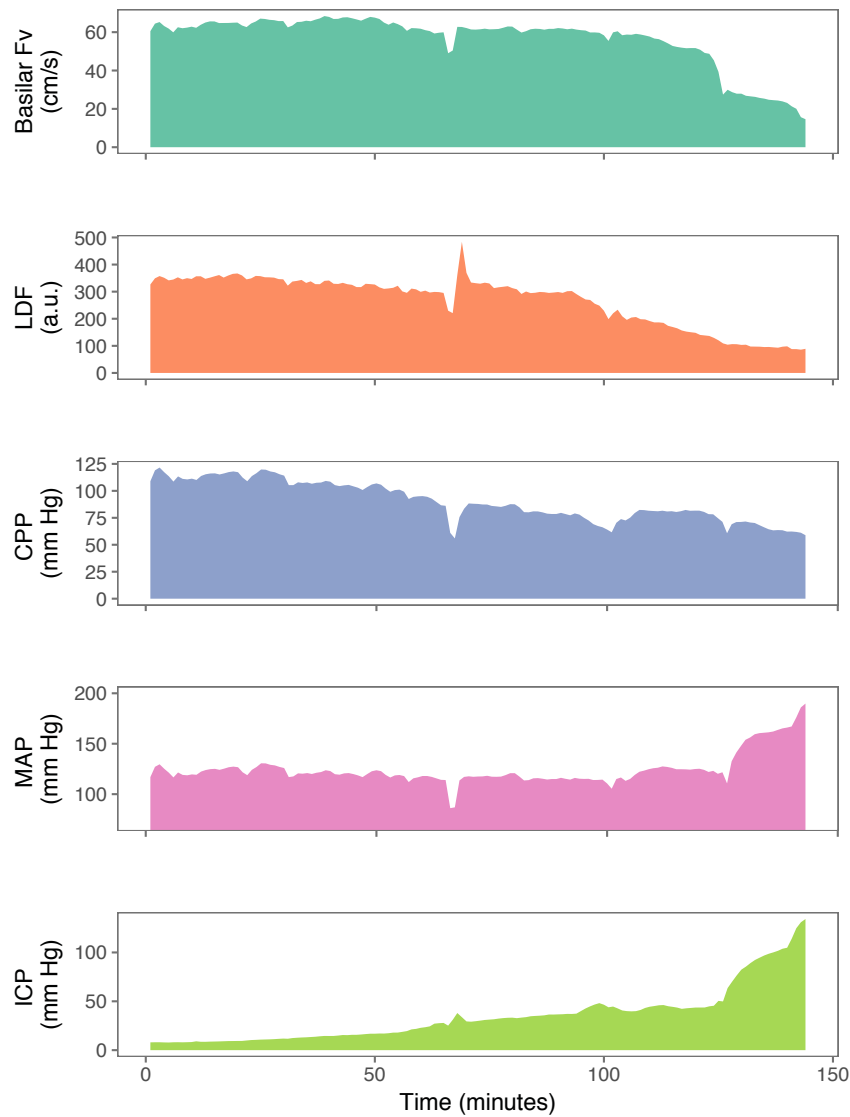
Figure 6.1: **Measured haemodynamic response to lumbar CSF infusion in the rabbit.** ICP was increased over the period of 30 minutes from baseline (10 mm Hg) to extreme levels (>100 mm Hg). LDF (top panel) decreased with this increasing ICP, whereas Fv in the basilar artery remained stable until ICP was above 50 mm Hg. Mean arterial blood pressure increased when ICP increased above 50 mm Hg as part of the Cushing reflex. *LDF* laser Doppler flowmetry; *Fv* flow velocity in the basilar artery, *MAP* mean arterial blood pressure; *CPP* cerebral perfusion pressure; *ICP* intracranial pressure.
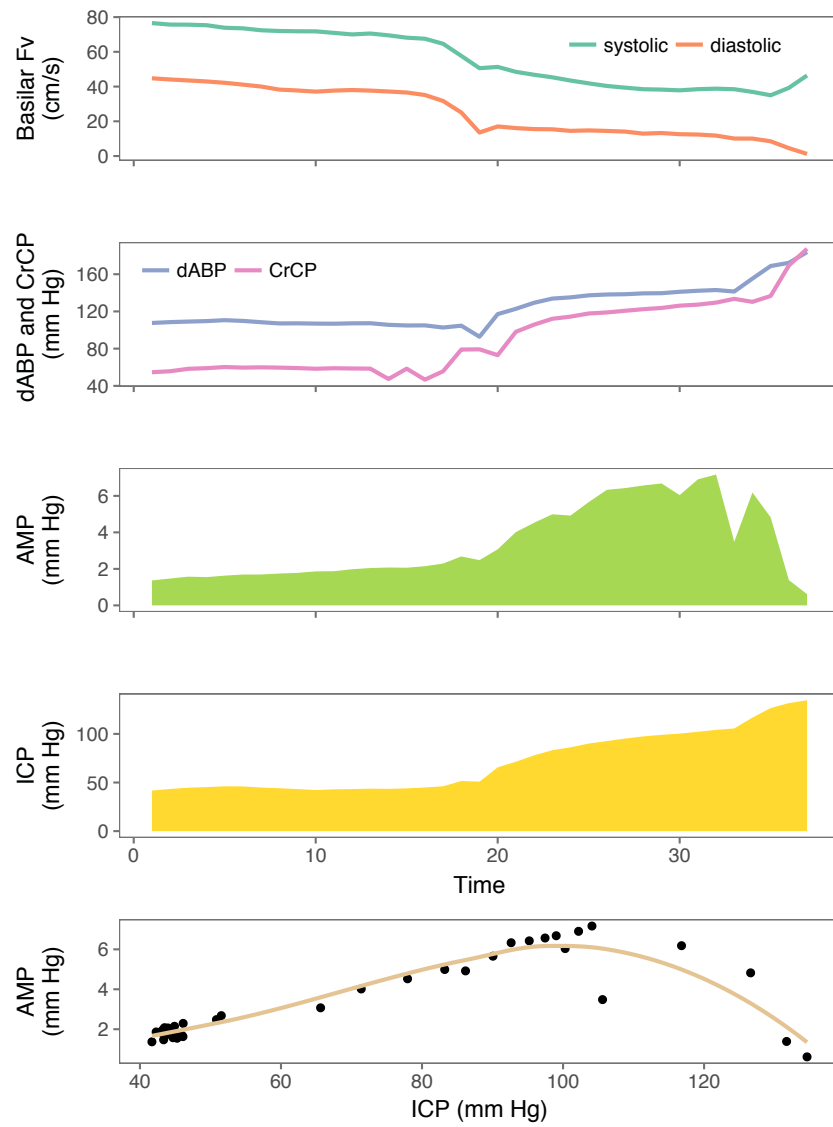
Figure 6.2: **Derived haemodynamic parameters in response to lumbar CSF infusion in the rabbit.** In the same rabbit as the previous figure, progressive increases in ICP caused an increase in CrCP, and diastolic ABP, as well as a corresponding decrease in the difference between them – the diastolic closing margin (second panel). At very high ICP, CrCP approached ABPd, which was associated with a drop of diastolic flow velocity to zero (top panel). AMP of ICP increased along with mean ICP until very high ICP, at which point AMP began to decrease (third panel). *CrCP* critical closing pressure; *dABP* diastolic arterial blood pressure; *Fv* flow velocity in the basilar artery; *AMP* pulse amplitude of ICP; *ICP* intracranial pressure.
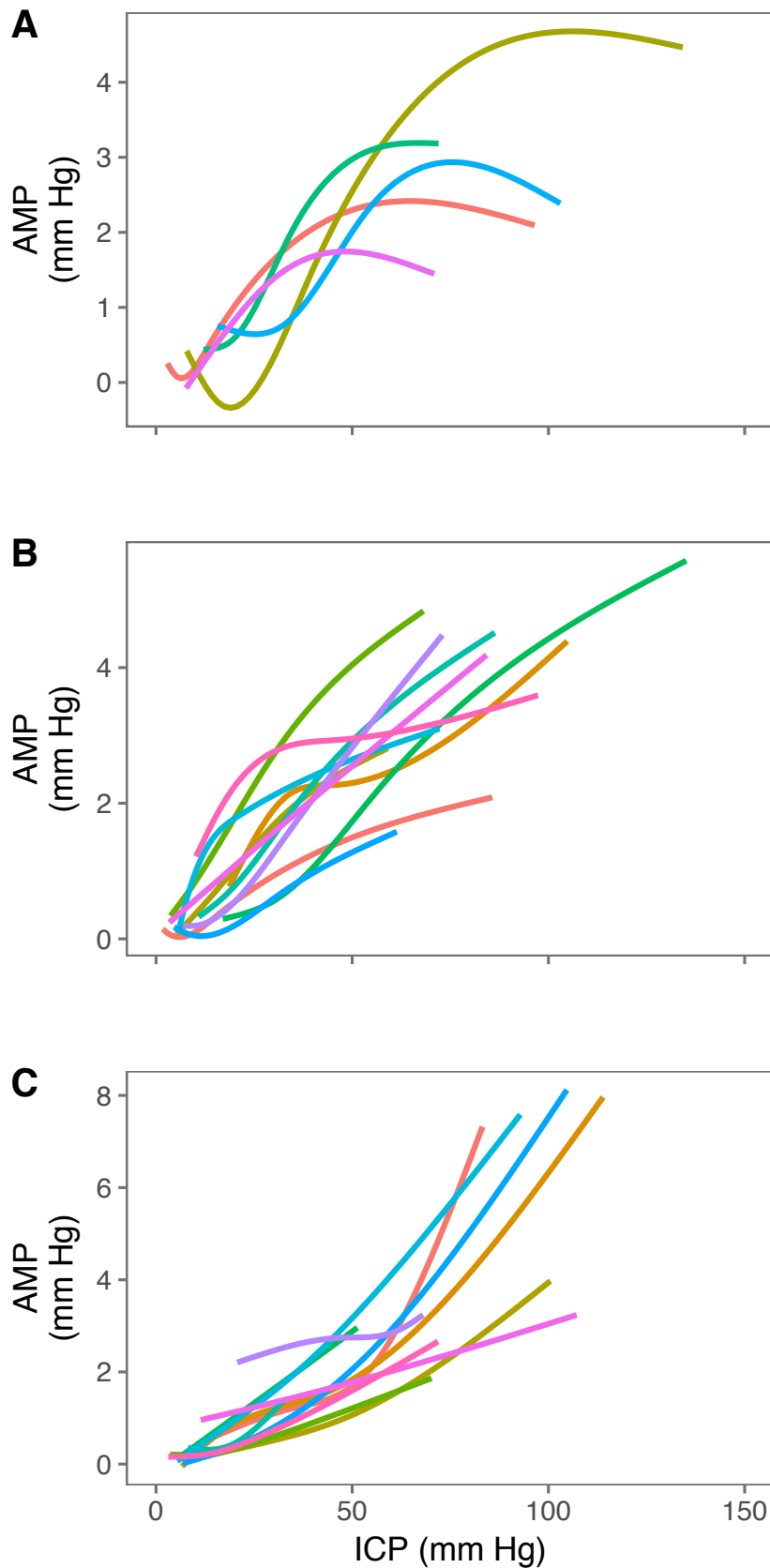
Figure 6.3: **Upper breakpoint of intracranial mean pressure-amplitude relationship.** In 5 rabbits, an upper breakpoint of the intracranial mean pressure-amplitude relationship was observed whereby further increases in mean ICP resulted in decreases in the pulse amplitude of ICP (panel A). 11 rabbits displayed a right deflected curve (panel B) and the remainder (11) a monotonic increase in AMP with increasing mean ICP (panel C). *ICP- intracranial pressure; AMP- pulse amplitude of ICP.*

Table 6.1: Physiologic summary of experimental cohort (mean (sd))

	Baseline ICP	Elevated ICP	Severe ICP	p (Elevated vs Baseline)	p (Severe vs Elevated)
ICP (mm Hg)	13.98 (4.36)	36.56 (3.55)	68.01 (9.86)	<0.001	<0.001
AMP (mm Hg)	0.59 (0.48)	1.62 (0.63)	3.04 (0.97)	<0.001	<0.001
Fv mean	45.43 (16.04)	43.77 (14.83)	35.34 (12.96)	0.62	<0.001
Fv diastolic	32.61 (13.94)	30.43 (13.03)	21.57 (11.34)	0.45	<0.001
Fv systolic	64.60 (19.60)	63.00 (17.61)	54.76 (14.52)	0.68	<0.001
LDF (% of first value)	94.29 (17.37)	68.94 (31.41)	40.34 (25.53)	<0.001	<0.001
WT (mm Hg)	17.61 (9.07)	9.01 (6.06)	8.16 (5.79)	<0.001	0.62
CPP (mm Hg)	71.62 (18.97)	54.11 (13.65)	42.17 (11.08)	<0.001	<0.001
MAP (mm Hg)	85.60 (18.12)	90.73 (14.24)	110.00 (15.61)	0.03	<0.001
aABP (mm Hg)	15.52 (4.36)	15.89 (4.13)	14.79 (4.33)	0.41	0.04
HR (bpm)	267.05 (38.13)	267.37 (33.07)	242.93 (41.46)	0.95	<0.001
CrCP (mm Hg)	31.41 (9.55)	45.54 (7.22)	75.88 (12.67)	<0.001	<0.001
$P_{ET}CO_2$ (mm Hg)	33.44 (9.07)	32.82 (5.61)	33.36 (4.97)	0.58	0.71

ICP intracranial pressure; *AMP* pulse amplitude of ICP; *Fv* flow velocity (basilar artery); *LDF* laser Doppler flowmetry (cortex); *WT* wall tension; *CPP* cerebral perfusion pressure; *MAP* mean arterial pressure; *aABP*- pulse amplitude of arterial pressure; *HR* heart rate; *CrCP* critical closing pressure.

Table 6.1 outlines recorded and derived parameters at baseline (~14 mm Hg), at elevated (~37 mm Hg), and severe (~68 mm Hg) levels of ICP. The Cushing response is reflected by the marked increase in ABP, and decrease in heart rate between elevated and severe ICP, and also between baseline and elevated in ICP. The Cushing vasopressor response occurred in 25 out of 27 experiments and was initiated at an average ICP of 26.2

mm Hg (range 10 to 45 mm Hg). As a result of the Cushing vasopressor response, despite an increase in ICP by 30 mm Hg between the elevated and severe ICP conditions, CPP only decreased by 12 mm Hg (table 6.1). Mean flow velocity of the basilar artery was not significantly changed from baseline to elevated ICP, whereas cortical LDF decreased by 30% Estimated vascular wall tension decreased from baseline to elevated ICP. Consistent with the increased ICP, CrCP increased throughout the infusion. End-tidal CO_2 did not change significantly during the experiment.

The comparison of cortical LDF and basilar artery Fv in response to raised ICP is shown in figure 6.4. This demonstrates that cortical LDF was more sensitive to increases in ICP than global basilar artery Fv. When expressed as a function of CPP, we see a similar response (figure 6.4).
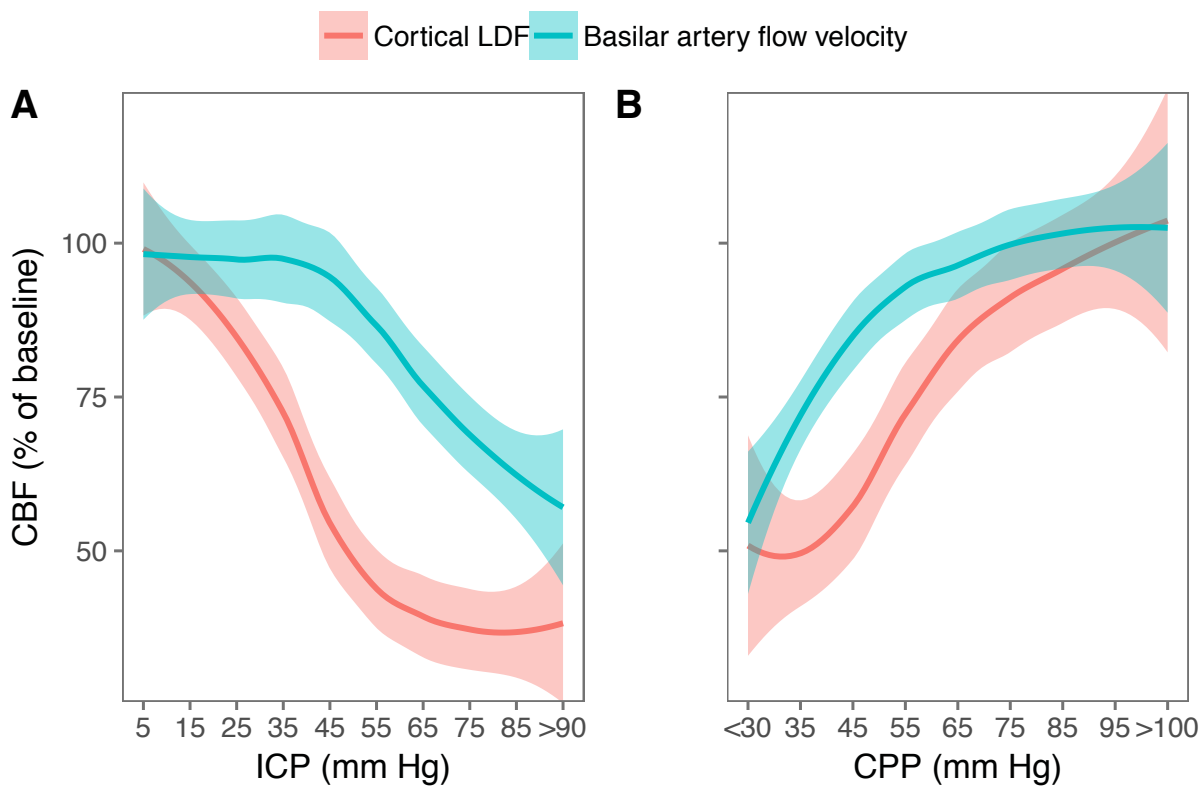
Figure 6.4: **Cerebral blood flow during increases in ICP referenced to ICP (A), or CPP (B).** Lines represent smoothed (LOWESS) function and its standard error across the 27 rabbits. Cortical LDF appears more sensitive to increases in ICP than basilar artery Fv. In panel B, again, LDF appears most sensitive to decreases in CPP. *CBF* cerebral blood flow; *Fv* flow velocity in the basilar artery; *LDF* laser Doppler flowmetry.

The interrelationships between changes in ICP, CBF, vascular wall tension, ABP, CPP and HR are shown in figure 6.5. CBF appears well maintained until ICP reaches values above 50 mm Hg. This maintenance of CBF was contributed by both decreases in wall tension and increases in ABP. Wall tension progressively decreased with increasing ICP particularly during early increases in ICP. At the highest levels of ICP, WT started to

increase.
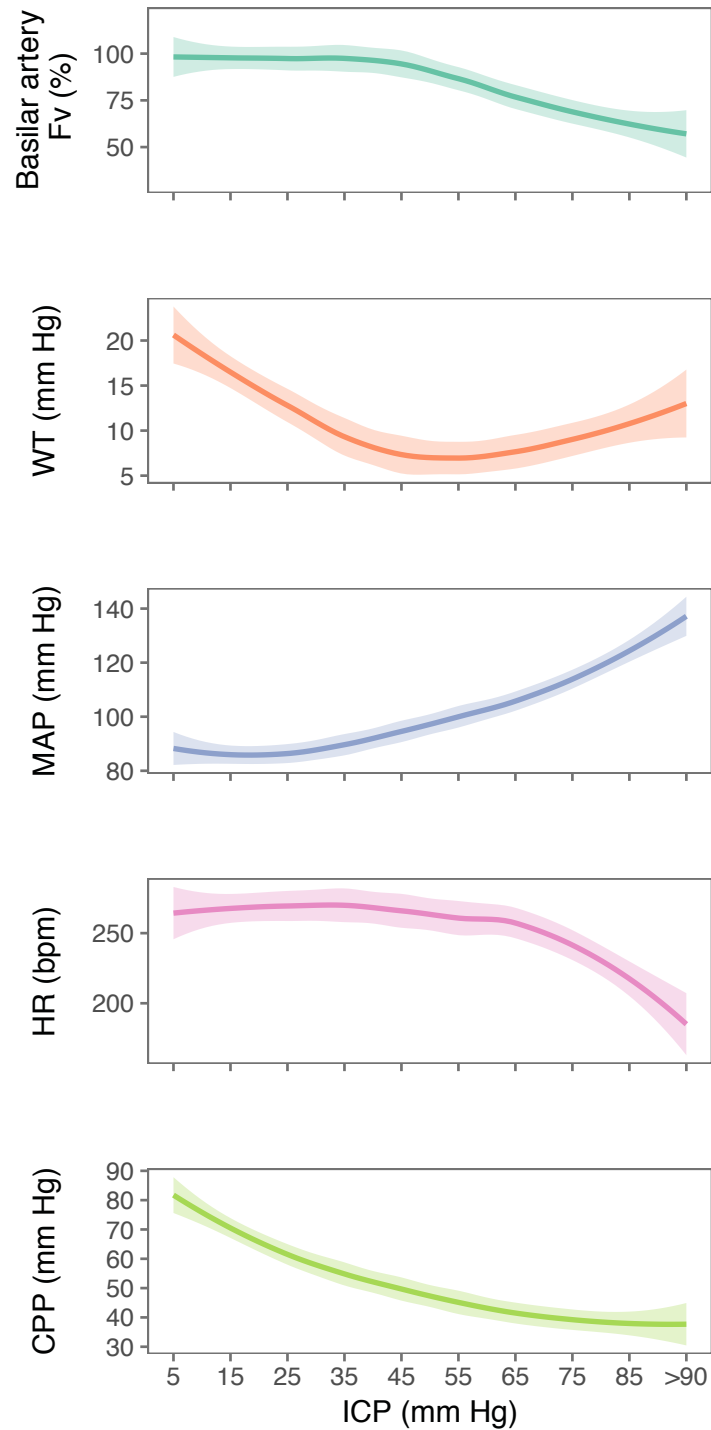
Figure 6.5: **Cerebral haemodynamic response to increasing ICP.** Global (basilar artery) Fv was well maintained until an ICP of 55 mm Hg (top panel). This maintained Fv was achieved by both a decrease in wall tension and an increase in ABP (panel 2 and 3). HR did not show major changes until relatively high ICP (60-75 mm Hg; panel 4). As a consequence of the vasopressor response, CPP was relatively buffered especially during large increases in ICP. *Fv* flow velocity; *WT* wall tension; *MAP* mean arterial pressure; *HR* heart rate; *CPP* cerebral perfusion pressure.

6.1.4 Discussion

By recalculating this experimental data we detailed three key insights into the cerebrovascular response to raised ICP. First, two intrinsic and mechanistically distinct compensatory adaptations to raised ICP were observed; with moderate increases in ICP, cerebral blood flow was maintained by decreases in vascular wall tension whereas with severe increases in ICP, cerebral perfusion was protected by the Cushing vasopressor response that maintained CPP and helped to keep cerebral vessels open. Second, regional differences in the control of cerebral perfusion seem to exist with cortical blood flow being more sensitive to an increase in ICP than global blood flow. Third, at dramatically high ICP (and low CPP) decreases in the amplitude of ICP pulsations can be observed. Herein we discuss the possible physiologic underpinnings and clinical implications of these observed phenomena.

ICP-dependent cerebroprotection; vascular wall tension and the Cushing response.

During increases in ICP, global CBF appeared to be maintained until ICP was above 50 mm Hg (figures 6.4 and 6.5). CBF was maintained by two mechanisms; a decrease in vascular wall tension and increases in MAP. During moderate increases in ICP, vascular wall tension progressively decreased (figure 6.4, table 6.1). This decrease in wall tension represents a decreases in vasomotor tone in response to a decreased cerebral perfusion pressure and thus is an autoregulatory response. Similar decreases in calculated wall tension have also been described in response to hypercapnia, arterial hypotension, and plateau waves of ICP[238,239]. During the increase in ICP, wall tension seemed to reach a minimum around ICP of 40 mm Hg and then did not significantly change with further increases in ICP (figure 6.5, table 6.1). This may represent a condition of maximum vasodilation imposed by the rigid collagen fibres in the tunica adventitia[240].

Further increases in ICP caused a vigorous Cushing response with MAP in some rabbits rising by > 50 mm Hg. This hypertensive response was most obvious at severely increased ICP but importantly was also present in many cases between baseline and elevated ICP. This may indicate that the ICP induced increases in ABP may play a protective role in maintaining perfusion rather than merely signifying irreversible neurologic damage. In support of this finding, a similar increase ABP in humans has been observed at even moderate ICP during lumbar CSF infusion studies[156,241].

Although it has been over 100 years since Harvey Cushing described this response[235], whether it is beneficial or detrimental is unclear[242]. The current data indicate two possible mechanisms by which the vasopressor response may be beneficial. First by increasing the ABP, CPP -the driving pressure for CBF- is maintained. Second, by increasing the intravascular pressure, the vessels are more resistant to the collapsing force of ICP (i.e. the difference between the ABP and the critical closing pressure is maintained). Critical closing pressure represents the ABP at which CBF would cease and is the sum of two 'closing' forces acting on the vessel; ICP and wall tension[240]. The difference between the

'opening' force ABP and closing 'force' of CrCP is the force that keeps vessels open and has been denoted the 'closing margin'[243]. If this closing margin is reduced to zero, vessels will collapse resulting in cessation of flow. By increasing ABP, the Cushing vasopressor response acts to maintain this closing margin.

In cases where despite the Cushing response, closing margin during diastole is equal to zero we see a complete cessation of cerebral diastolic flow (figure 6.2). The abolition of the diastolic closing margin seems to have two consequences observable with haemodynamic monitoring; zero diastolic flow due to diastolic collapse and an upper-breakpoint of the amplitude- mean pressure relationship 6.3. Such an 'upper breakpoint' of the typically monotonic relationship between pulse amplitude and mean ICP has been described previously during intracranial hypertension following traumatic brain injury[244] and has been considered in clinical practice as an important landmark of intracranial hypertension, above which normal cerebral haemodynamic regulation fails and acute ischaemia may contribute heavily to brain damage[231].

Thus, it seems that the brain has two intrinsic mechanisms to protect itself from hypoperfusion during intracranial hypertension; decreases of arterial wall tension early increases in ICP and a Cushing vasopressor response that predominates at extreme levels of ICP. A practical application is that these intrinsic mechanisms are the main therapeutic measures that can be used to adjust CBF; decreasing vascular wall tension (using pharmacological or ventilator intervention), or increasing ABP (using vasopressors). However, inspection of figure 6.5 indicates that the efficacy of each intervention may depend on cerebrovascular factors that are only appreciated through multimodality monitoring; if wall tension is already close to zero, further attempts at vasodilation are unlikely to improve perfusion as the vessels may already be maximally dilated. In these situations, increasing ABP may be the only viable way to increase CBF.

Differential control of cortical compared to global blood flow

Using in-vivo global and cortical CBF measurement during dynamic changes in ICP, we demonstrated that cortical blood flow decreased almost linearly with increasing ICP whereas global flow (basilar artery flow velocity) was well maintained until a high ICP (~50 mm Hg). Other studies in rats have not observed this phenomenon[233,234], raising the possibility that this decrease in LDF flux could have been caused by an experimental factor such as by displacement of the the LDF probe during CSF infusion. However, the LDF probe was secured at the burr-hole in attempt to eliminate any probe displacement and several lines of evidence support a 'cortical vascular vulnerability' to increased ICP.

A potential explanation for the vulnerability of cortical compared to global CBF could lie in a differential vascular reactivity of cortical compared with non-cortical brain. Such a discrepancy could theoretically result in a 'vascular steal' phenomena whereby, during periods of reduced cerebral perfusion pressure, vessels within actively autoregulating sub-cortical areas dilate, while those in the cortex would not change caliber. This topographic

difference in resistance would result in CBF being diverted away from the cortex. In support of a topographic differences in autoregulatory capacity, Horsefield et al. demonstrated an intrinsic difference in the autoregulatory efficiency of the grey matter compared to white matter of healthy humans[245]. They demonstrated that in response to a transient decrease in CPP induced by leg cuff release, CBF recovered more quickly in the white matter compared to the grey matter.

Further support for a differential autoregulatory capacity of the cortex compared to non-cortical areas comes from clinical monitoring studies. In a group of severe TBI patients with monitored ABP, ICP, LDF and middle cerebral artery Fv, Zweifel et al., assessed the correlation between slow changes in CPP and slow changes in CBF[71]. In this situation, there was a higher correlation between CPP and LDF than between CPP and middle cerebral artery Fv. The authors concluded that the cortex may be more vulnerable to spontaneous changes in CPP. From a teleological point of view, such cortical sensitivity to high ICP could be a mechanism for diverting blood flow to areas of the brain most crucial for survival; the brainstem cardiorespiratory nuclei.

The mechanisms underlying this differential response are unclear. It could represent intrinsic differences in vascular biology or simply regional differences in the hydrodynamic response to CSF infusion. For example, an increase in ICP via a CSF infusion could cause a greater increase in ICP in regions closer to the CSF space, including the cortex. Regional impairment of CBF has been demonstrated in the periventricular spaces during CSF infusion in normal pressure hydrocephalus patients[246]. In that study, infusion of artificial CSF into the subarachnoid space resulted in a decrease in cerebral blood flow, most prominent in the watershed areas close to the ventricles. Whether such autoregulatory gradients to CSF infusion also exist in relation to distance from the subarachnoid spaces is unknown.

Relationship between ICP pulsatility and mean ICP

The relationship between pulse amplitude and mean ICP has been described many years ago[247] and is one of most well-known characteristics of ICP signal. It has been classically interpreted by loss of cerebrospinal compensatory reserve with increasing mean ICP, elegantly interpreted by exponential pressure-volume relationship. However, very early, Avezaat and van Eijndhoven observed a right side deflection point of the volume-pressure response at very high levels of intracranial pressure, experimentally studied with inflated epidural balloon[248]. The same phenomenon can be observed as upper breakpoint of the amplitude- mean intracranial pressure relationship, and has been observed clinically in rare cases of patients after TBI who died of refractory intracranial hypertension[244] or in a paediatric neurosurgical population[249]. It is an uncommon appearance, counterbalanced by Cushing increase of ABP, and its etiology is unclear. It could be related to terminal closing of the cerebral arterial bed when the critical closing pressure approaches the ABP.

Perspectives

The current study highlights that modest ($\pm$ 10 mm Hg) alterations in ICP have the potential to decrease cortical perfusion and decrease vascular wall tension. Thus, even in the controlled experimental condition, just knowing the ICP or CPP is unlikely to tell you whether the CBF is adequate. Probably only by integrating global (ICP, CPP, pressure reactivity, Doppler derived wall tension, CrCP and Fv) and local (microdialysis, brain oxygen pressure) physiologic markers will we be able to adequately understand the state of the patients cerebral circulation and how it may be optimized.

Limitations

Neither LDF or basilar artery flow velocity measure volumetric flow. This is especially relevant for the basilar artery measurements, where a maintained flow velocity during raised ICP could be contributed to by a reduction in diameter of the insonated vessel and thus reduced volumetric flow. Further, application of cortical LDF during an infusion of fluid into the subarachnoid space raises the possibility of LDF probe displacement by the infusion. Although gross displacement of the LDF probe could easily be ruled out visually, subtle changes in orientation of the LDF probe would be more difficult to detect. Despite this caveat, the sensitivity of LDF to changes in CPP is consistent with the impaired cortical autoregulation described in a previous LDF study in traumatic brain injured patients[71].

The experimental paradigm involved clamping of the common carotid artery prior to experimentation, which could affect cerebral haemodynamics *per se.* However, no neurological deficit was observed in these rabbits after clamping and rendering the rabbits basilar artery dependent ensured that flow velocity measured at the basilar artery represented a global cerebral perfusion. Finally the current analysis is derived from the digital recordings of experiments performed and published in the past[236,250]. Although this is a limitation, it can be argued that the multiple use of experimental material to conduct mathematical modeling studies is scientifically and ethically sound because it takes full advantage of recent advances in physiologic mathematical modeling while limiting the number of animals that need to be sacrificed

Conclusion

The brain attempts to compensate for an increased ICP by reducing vascular wall tension and increasing ABP in an ICP dependent manner. In addition, cortical perfusion appears to be exquisitely sensitive to increases in ICP and this may not be detected by global measures of perfusion.

6.2   Observations on the cerebral effects of refractory intracranial hypertension after severe traumatic brain injury

6.2.1   Introduction

Raised intracranial pressure can occur due to an expanding mass lesion or due to increases in volume of any of the vascular, CSF, or parenchymal compartments within brain[173]. The detrimental effects of raised intracranial pressure are two-fold. One is the development of transtentorial pressure gradients that can cause focal ischaemia of vital brain stem centres leading to rapid death. The second is that increased ICP causes an increase in cerebral venous pressure by compression at the level of the bridging veins, leading in turn to a decrease in cerebral perfusion pressure and global cerebral hypoperfusion[11,251].

Surprisingly, the cerebral physiological sequelae of raised ICP secondary to TBI are unclear. As shown in section 6.1, increased ICP decreases cerebral blood flow, raises arterial blood pressure, and modifies the ICP pulse characteristic. However, whether these findings translate to the complex situation of raised intracranial pressure after severe traumatic brain injury is uncertain.

In this study, we sought to describe the cerebral oxygenation, cerebrovascular pressure reactivity and ICP pulse amplitude response to severe and sustained intracranial hypertension after severe TBI.

6.2.2   Methods

Patients

From a database of 1146 severe TBI patients entering the neurocritical care unit (NCCU) at Addenbrooke's hospital with computerized ICP monitoring, files were selected that contained an initial ICP less than 25 mm Hg with a subsequent ICP rise to over 40 mm Hg for at least an hour. This yielded 37 suitable files. The computerized data storage protocol was reviewed and approved by the local ethics committee of Addenbrooke's Hospital, Cambridge University and the neuro critical care unit User's Group. For patients admitted after 2000, regional ethical approval was obtained (30 REC 97/291) for anonymised data recording. Patients were managed according to TBI guidelines[14] aimed at keeping ICP < 20 mm Hg and CPP > 50-60 mm Hg.

Data Acquisition and Processing

ICP was monitored with an intraparenchymal sensor (Codman ICP Micro- Sensor, Codman & Shurtleff, Raynham, MA). Arterial blood pressure (ABP) was zeroed at the level of the right atrium (Baxter Health- care CA, USA; Sidcup, UK). No corrections were made for hydrostatic pressure influence. Brain tissue oxygenation was monitored using a Licox

probe via a cranial access device (Technicam, Abbott, UK). Probes were positioned at a constant depth in the white matter, pericontusional in focal injuries or in the non-dominant frontal lobe in diffuse injuries. Probe positioning was verified by means of a head computed tomography (CT) scan.

All data were sampled at least 50 Hz with proprietary data acquisition and analysis software (ICM 1991-2002[244] and then with ICM+©,`http://www.neurosurg.cam.ac.uk/icmplus` after 2002). HR was determined as the fundamental frequency of the ABP signal over a 10 second window within the cardiac (40-180 cycles/min) frequency band. Amplitude of the cardiac pulse in ICP and ABP were determined as the fundamental amplitude in the cardiac frequency band (40-180 cycles/min). ABP and ICP signals were averaged (mean) over a 10-second window then PRx was calculated as the moving Pearson correlation of 30 consecutive ABP and ICP, updated every minute. RAP was calculated similarly as the moving correlation between mean ICP and the pulse amplitude of ICP. AMP was divided by aABP (giving AMP:aABP ratio) to get an indication of the transmission of the cardiac pulse from the blood pressure to the intracranial pressure.

ICP, ICP pulse amplitude, ABP, ABP pulse amplitude, and RAP data were available for all 37 patients, while PRx and $P_{BT}O_2$ were available for 24 and 9 patients respectively.

Statistical analysis

Data are reported as means and standard deviations. The relationship between minute-by-minute values of mean ICP and ICP pulse amplitude was fitted with a generalised additive model allowing for 3 different segments (cubic regression spline smooths). The number of segments (3) was chosen *a priori* to allow for 3 different portions of the ICP, AMP relationship (~flat at low ICP, steep rising segment, and an upper breakpoint).

For the aggregate relationship between ICP or CPP and intracranial parameters (PRx, RAP, AMP), the means of each variable from each patient were calculated in 10 mm Hg wide intervals of ICP and CPP and then local regression smoothing (LOWESS) was applied. This binning procedure, prior to lowess fitting was to ensure that patients with longer recordings did not contribute disproportionately to parts of the smooth. Pairwise comparisons between physiological variables at the different ICP levels were performed using students t-test. No adjustments for multiple comparisons were made in this exploratory analysis. To test whether early PRx was different between those who developed refractory high ICP and TBI patients who did not, we first identified controls for the 24 cases who had simultaneous ICP and PRx data with 24 controls (selected from the 1146 patients) who were matched for sex, initial GCS and age. Then we performed a Wilcox test for the ICP values between the two groups. We used the R language and software environment for statistical computation (R Core Team 2015 version 2.12.1[147]) using the following packages: dplyr[149], ggplot2[150], gam[252] and MatchIt[253]. The significance level was set at 0.05.

6.2.3 Results

Admission characteristics are displayed in table 6.2. Of the 37 patients, 8 were female and the mean age was 30.47. In the cohort, ICP rose from a mean minimum of 5.56(5.99) to a mean maximum of 76.55(23.52). 18 of the patients died.

Two patient examples illustrating the heterogeneous nature of the response to intracranial hypertension are depicted in figure 6.6. In the patient on figure 6.6A, PRx is initially preserved and only becomes impaired after the development of raised ICP. In the other patient (figure 6.6B), PRx is clearly disturbed prior to the development of severe refractory raised ICP. In this case, a decrease in $P_{BT}O_2$ followed the decrease in CPP almost linearly to reach oxygen pressures of less than 5 mm Hg. In addition, a dissociation between the rise in mean ICP and pulse amplitude of ICP can be seen near the end of the recording, such that with increasing ICP, pulse amplitude remained constant. This failure for ICP pulse amplitude to increase despite increases in mean ICP has been postulated to be due to critical cerebrovascular collapse.

Table 6.2: Patient demographics; cerebral effects of refractory intracranial hypertension after TBI

	Overall
n	37
Age [years] (mean (sd))	30.47 (12.38)
Sex (%)	
female	8 (21.6)
male	27 (73.0)
NA	2 (5.4)
GCS <= 8 (%)	
FALSE	5 (13.5)
TRUE	28 (75.7)
NA	4 (10.8)
Monitoring length [hours] (mean (sd))	181.62 (141.89)
Decompressive craniectomy (%)	
FALSE	20 (54.1)
TRUE	11 (29.7)
NA	6 (16.2)
ICP [mm Hg] (mean (sd))	26.34 (9.98)
Max ICP [mm Hg] (mean (sd))	76.55 (23.52)
Min ICP [mm Hg] (mean (sd))	5.56 (5.99)
CPP [mm Hg] (mean (sd))	66.07 (13.31)
PRx [a.u.] (mean (sd))	0.19 (0.28)
Mortality (%)	
alive	16 (43.2)
dead	18 (48.6)
NA	3 (8.1)

GCS Glasgow coma scale; *ICP* intracranial pressure; *CPP* cerebral perfusion pressure; *PRx* pressure reactivity index.
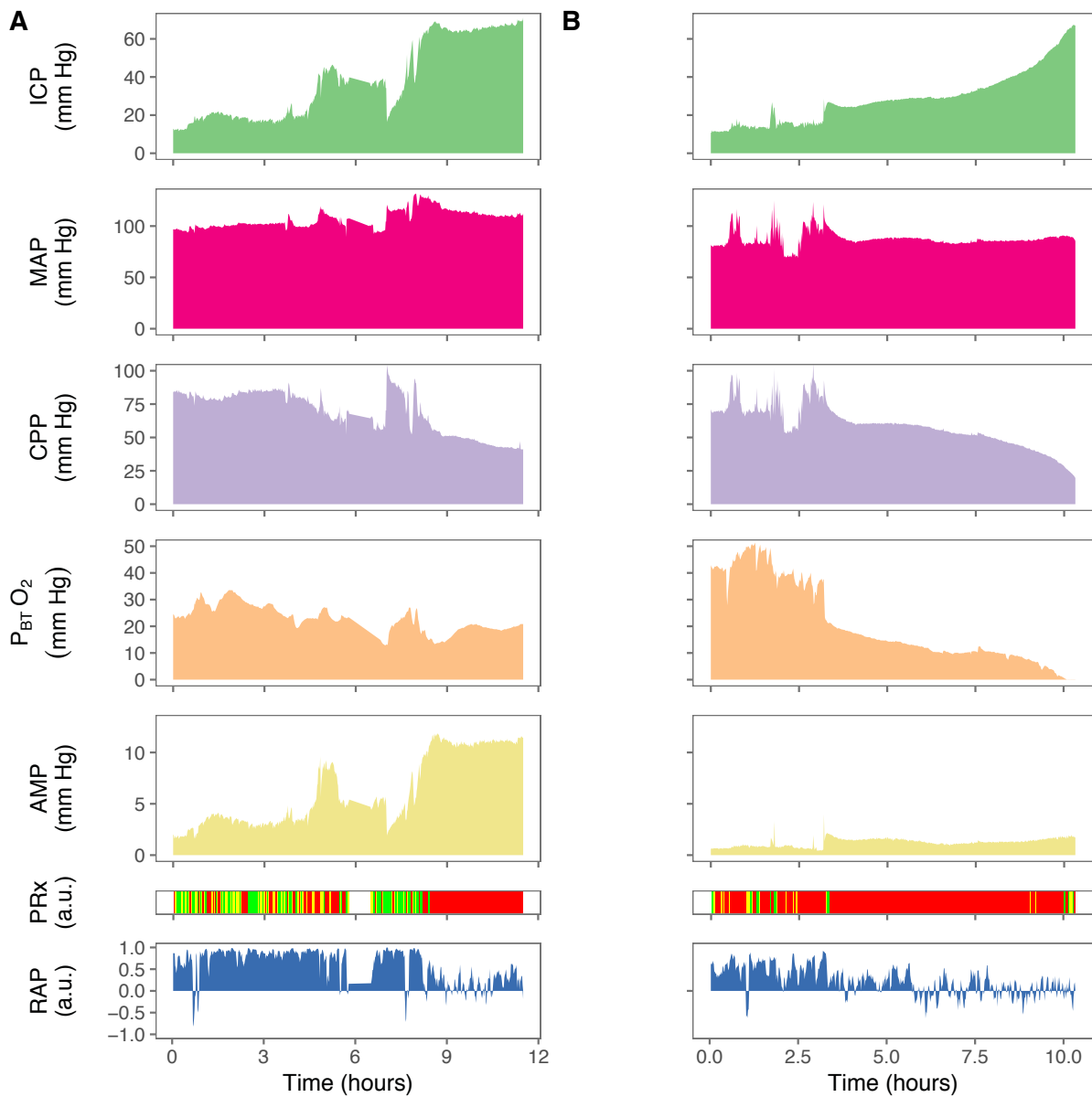
Figure 6.6: **Neuromonitoring during severe intracranial hypertension in two traumatic brain injured patients.** On the right, ICP rises dramatically from below 20 mm Hg to over 60 mm Hg in the space of 10 hours. This increase in ICP was associated with a fall in CPP, and brain tissue oxygenation. In this case, PRx was disturbed (>0.25) even in the first 3 hours while ICP was under 20 mm Hg. Despite large increases in ICP over the last 5 hours, pulse amplitude of ICP (yellow) shows little change. On the left, ICP rises similarly to 70 mm Hg over a period of 12 hours. In contrast to the monitoring on the right, PRx was not significantly impaired prior to the increase in mean ICP. In addition, although $P_{BT}O_2$ decreased with increasing ICP, it did not reach severely hypoxic values even during the maximal mean ICP ($P_{BT}O_2 \sim 20$ mm Hg at ICP 60 mm Hg). These two cases illustrate that refractory intracranial hypertension may have different neuromonitoring phenotypes. *ICP* intracranial pressure; *AMP* pulse amplitude of ICP; *MAP* mean arterial pressure; *CPP* cerebral perfusion pressure; $P_{BT}O_2$ brain tissue oxygenation; *PRx* pressure reactivity index; *RAP* cerebrospinal compensatory reserve.

Table 6.3: Physiologic response to high intracranial pressure after TBI (mean (sd))

Variable	0-25 mm Hg	25-50 mm Hg	50-150 mm Hg	p (elevated vs base)	p (severe vs elevated)
ICP (mm Hg)	17.39 (3.77)	32.93 (2.58)	62.27 (11.43)	<0.001	<0.001
AMP (mm Hg)	1.88 (1.38)	3.21 (2.35)	5.10 (4.08)	0.009	<0.001
AMP:aABP [a.u.]	0.10 (0.06)	0.16 (0.10)	0.29 (0.22)	0.015	<0.001
CPP (mm Hg)	73.50 (9.43)	62.88 (10.80)	35.74 (20.51)	<0.001	<0.001
MAP (mm Hg)	90.89 (9.79)	95.83 (9.58)	97.57 (13.56)	0.013	0.37
aABP (mm Hg)	18.90 (3.22)	19.58 (4.21)	19.49 (5.78)	0.258	0.97
HR (bpm)	79.78 (16.09)	80.77 (19.52)	84.45 (20.01)	0.716	0.27
PRx (a.u.)	0.09 (0.29)	0.23 (0.33)	0.59 (0.25)	0.013	<0.001
RAP (a.u.)	0.52 (0.20)	0.56 (0.26)	0.46 (0.27)	0.386	0.03
$P_{BT}O_2$	27.27 (7.32)	20.78 (5.43)	12.68 (7.09)	0.06	0.02

ICP intracranial pressure; *AMP* pulse amplitude of ICP; *aABP* amplitude of arterial blood pressure; *MAP* mean arterial pressure; *CPP* cerebral perfusion pressure; *HR* heart rate; *PRx* pressure reactivity index; *RAP* cerebrospinal compensatory reserve; $P_{BT}O_2$ brain tissue oxygenation.

Across all patients, PRx (figure 6.7) showed a general increasing trend, signifying disturbed autoregulation with increasing ICP and of note, the PRx at baseline levels of ICP is disturbed in a number of the patients (appendix A, figure A.2). As expected, PRx plotted against CPP reveals a steadily increasing PRx with decreasing CPP. The relationship between mean ICP (and CPP) levels and ICP pulse amplitude is depicted in figures 6.8 and 6.9. In general, ICP amplitude increased monotonically with increasing mean ICP (11 patients; figure 6.8A), however in 7 of the cases an upper breakpoint (a switch from a positive to a negative relationship between mean ICP and ICP pulse amplitude) is seen at high intracranial pressures (figure 6.8A). In 17 patients, a right-ward deflection of the AMP-ICP was detected (figure 6.8B). In the remaining 2 patients, AMP monotonically decreased with increasing ICP (up until ICP 40 mm Hg - not included in figure). Similar responses were seen when ICP pulse amplitude was normalized to the arterial pulse amplitude (figure 6.9, middle panel). The index of cerebral compensatory reserve, RAP, increased from low to moderate levels of ICP, and thereafter showed a gradual decline with further increases in ICP (figure 6.9E). At all levels of ICP or CPP, the averaged RAP response was greater than + 0.3 a.u..
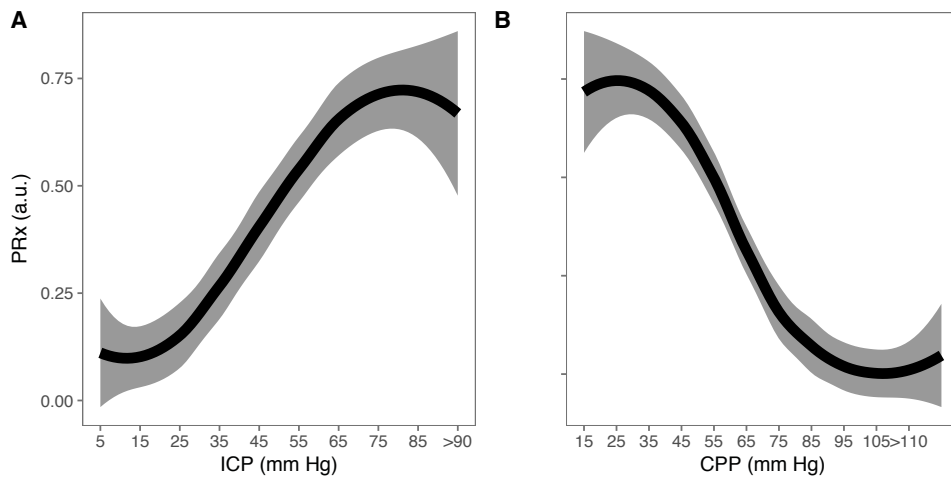
Figure 6.7: **PRx response to refractory intracranial hypertension expressed relative to changes in ICP (left) and CPP (right) (LOWESS with 95% confidence interval; n=24).** Pressure reactivity increased with increasing ICP and PRx plotted against CPP revealed a partial 'U-shaped' curve as previously described. PRx is well maintained until CPP drops below 70 mm Hg, below which PRx deteriorates. *PRx* pressure reactivity; *ICP* intracranial pressure; *CPP* cerebral perfusion pressure.

When all 9 available $P_{BT}O_2$ responses are viewed together (figure 6.10), $P_{BT}O_2$ shows a steady decrease with increasing intracranial pressure. However, the between patients response is strikingly variable (figure A.3). When $P_{BT}O_2$ is plotted against CPP, a consistent pattern is seen, all but one patient show a decrease in $P_{BT}O_2$ with decreasing CPP.

When compared to 24 controls (severe TBI patients, matched for age, sex and initial

GCS), initial mean PRx in the first five hours of monitoring was higher (figure 6.11) in the cases of refractory intracranial hypertension. While ICP was also higher, this did not reach statistical significance (Wilcox p=0.10).

Grouping each patients data into three ICP groups ($<$25, 25-50, $>$50 mm Hg; table 6.3), confirmed the visual interpretation of figures 6.7,6.8,6.10,6.9.
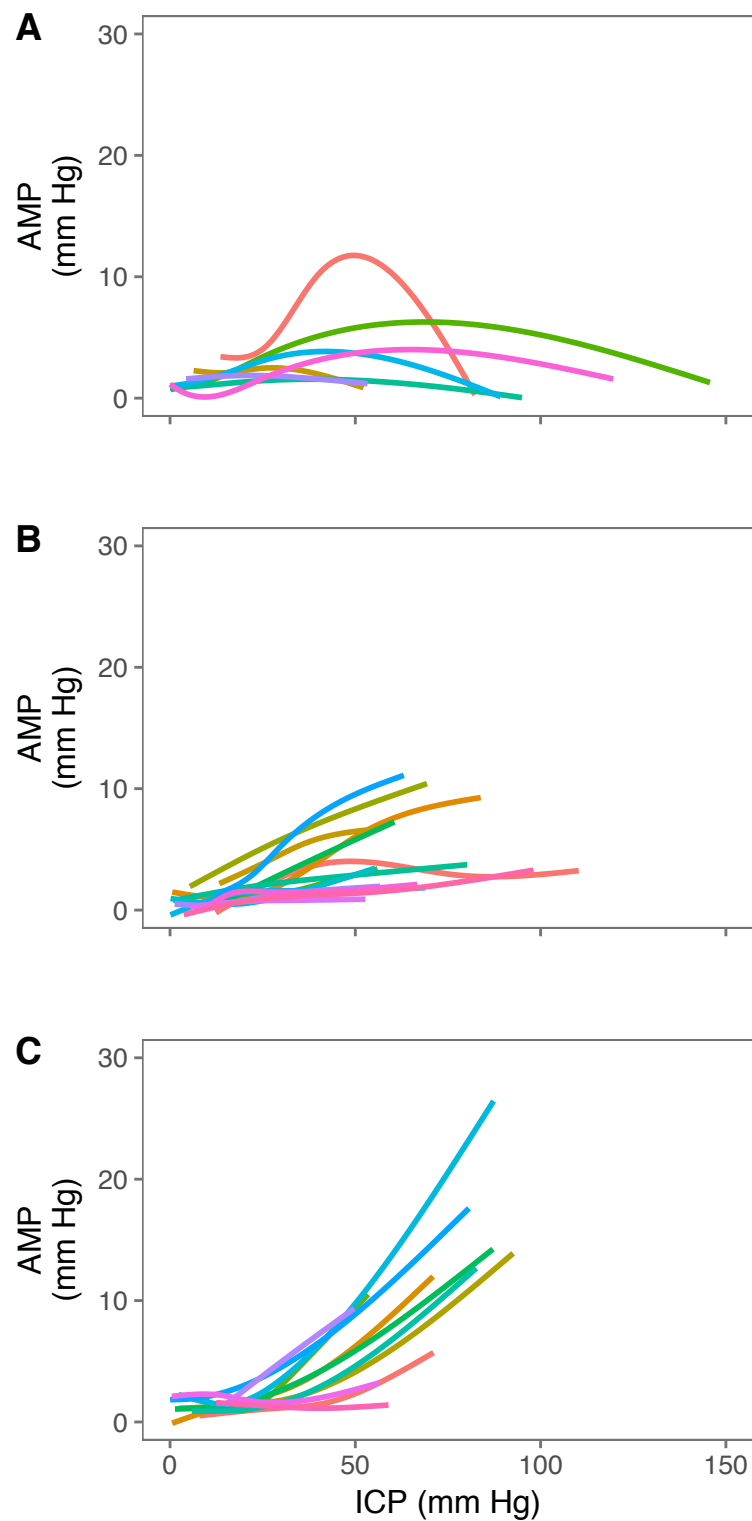
Figure 6.8: **The ICP amplitude - mean ICP relationship (n=37).** Three distinct patterns were identified; those with a monotonic increasing pattern (C), a rightward deflected pattern (B) or with an upper break point (A). *ICP* intracranial pressure; *AMP* pulse amplitude of ICP.
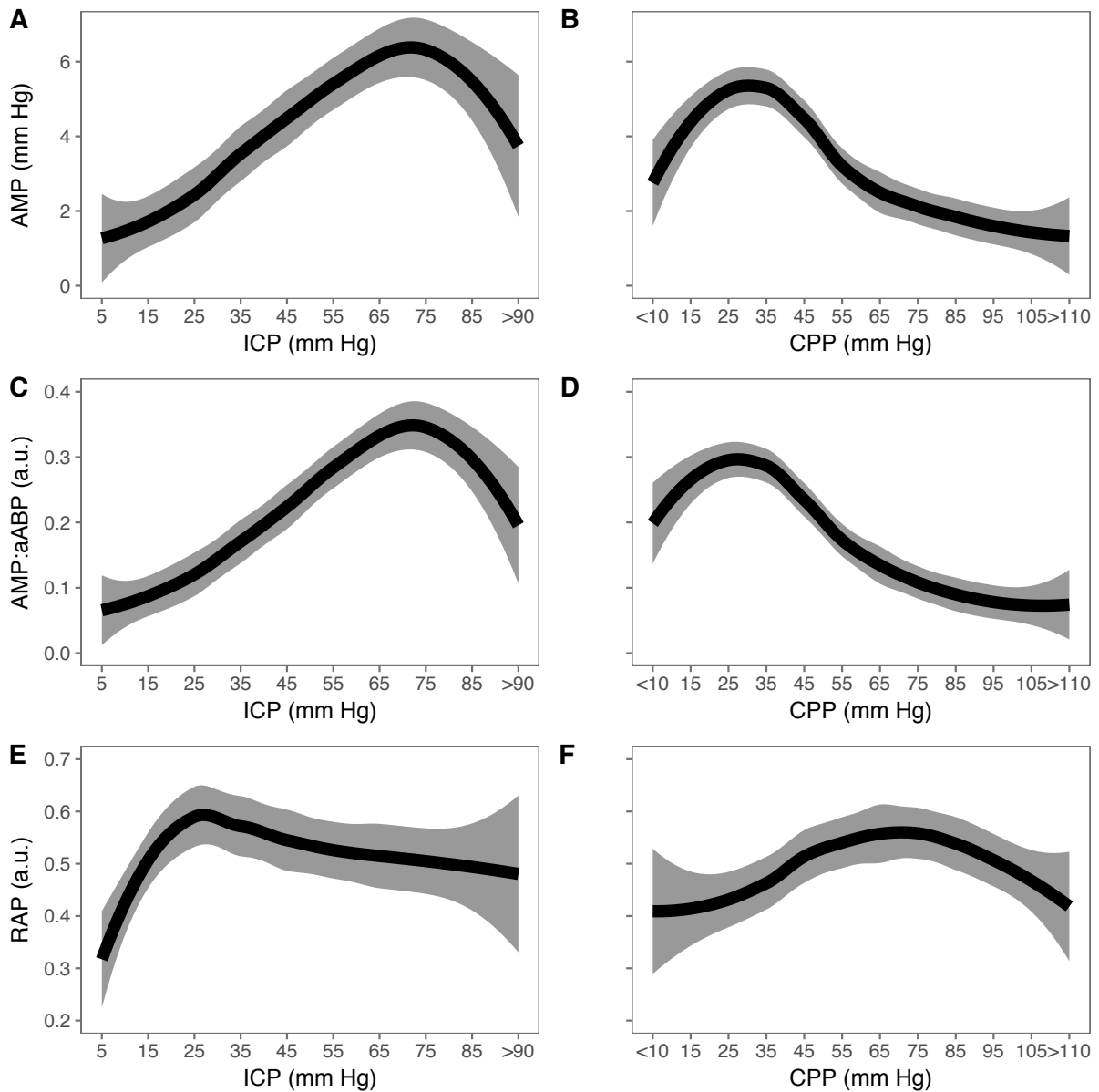
Figure 6.9: **Relationship between ICP (left) or CPP (right) with ICP amplitude, transmission of arterial to intracranial pulse, and RAP (LOWESS with 95% confidence interval; n=37).** When all patients are grouped together, an upper breakpoint in the AMP mean ICP relationship occurs at around 70 mm Hg. A similar response is seen for arterial to intracranial pulse transmission indicating that a decreased ABP amplitude is not responsible for the AMP- ICP upper breakpoint. RAP increases from low (0 mm Hg) to moderate ICP (~30 mm Hg) and thereafter decreases with further increase in ICP. *ICP* intracranial pressure; *CPP* cerebral perfusion pressure; *RAP* cerebral compensatory reserve.
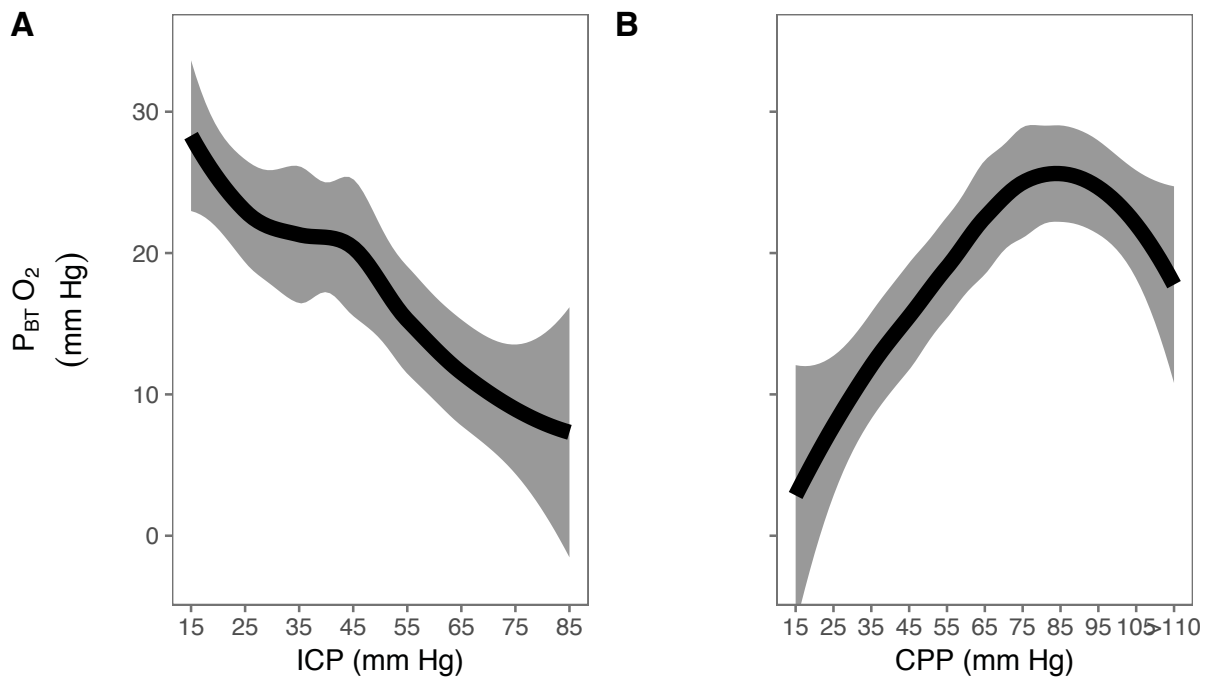
Figure 6.10: **P$_{BT}$O$_2$ response to refractory intracranial hypertension expressed relative to changes in ICP (left) and CPP (right) (LOWESS with 95% confidence interval; n=9).** When expressed against ICP, P$_{BT}$O$_2$ demonstrates a steady decrease. When expressed in relation to changes in CPP, the relationship resembles the autoregulation curve; with moderate levels of CPP (70- >90 mm Hg), oxygenation is well maintained, but lower than 70 mm Hg, oxygenation decreases (by approximately 0.5 mm Hg per 1 mm Hg decrease in CPP. *P$_{BT}$O$_2$* brain tissue oxygenation; *ICP* intracranial pressure; *CPP* cerebral perfusion pressure.
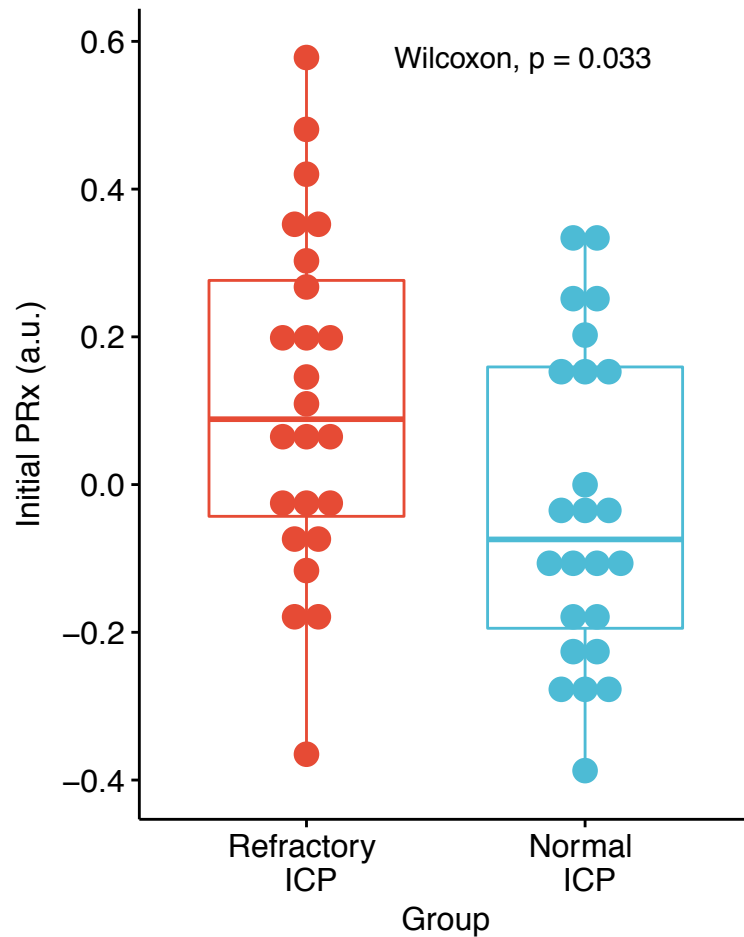
Figure 6.11: **PRx over the first 5 hours in patients who went on to develop severe refractory intracranial hypertension compared to severe TBI patients matched for age, sex and initial GCS.** Those who developed severe refractory intracranial hypertension tended to have higher PRx in the first 5 hours of monitoring (p=0.033) while ICP was not significantly different between the two groups (p=0.10). *PRx* pressure reactivity index; *ICP* intracranial pressure.

6.2.4 Discussion

By isolating the rare cases of severe refractory intracranial hypertension with multimodality monitoring we describe the cerebral physiological response to raised ICP after TBI. Although only exploratory, these data highlight the impact of raised ICP on cerebral autoregulation, the sensitivity of brain tissue oxygenation to raised ICP and the possible role of impaired pressure reactivity in identifying at risk patients.

Autoregulation parameters

Raised ICP impairs dynamic cerebral autoregulation (Figure 6.7, table 6.3). This confirms previous investigations of autoregulation during short term increases in ICP (plateau waves)[254,255] and is consistent with a recent large between patient analysis that found a

significant correlation between mean ICP over the whole monitoring period and mean PRx[256]. In contrast to these studies however, the current analysis observed changes *within* patients and over periods of time that are substantially longer than the calculation window for PRx. Therefore the finding of impaired PRx with increasing ICP is unlikely to be explained by between patient confounding factors or time-resolution limitations of the PRx method.

Perhaps most striking though, is that PRx was disturbed before the onset of intracranial hypertension in many of the patients. This has been observed previously in a cohort of brain injured patients of mixed pathologies (subarachnoid haemorrhage, hypoxic brain injury, trauma), but has not been statistically assessed[257]. After matching cases of severe refractory high ICP for age, initial GCS and sex, we found that PRx in the first five hours was higher in those who developed raised ICP. The same was not true for the mean ICP over the first five hours, although this did approach statistical significance (p=0.10). This potentially provides an explanation for the finding (see chapter 4) that time spent with impaired PRx but normal ICP or CPP is related to mortality and unfavourable outcome and further highlights the potential utility of continuous assessments of cerebral autoregulation in predicting raised ICP events. Encouragingly, a previous investigation found that a feature similar to PRx (the long term MAP-ICP correlation from low-frequency data) can help predict periods of raised ICP 30 minutes before they occur[258]. Identifying patients at risk of raised ICP may prove crucial as raised ICP carries a high risk of mortality, and perhaps the most effective ICP treatments such as decompression, require some time to mobilise.

In addition, we found a consistent increase in MAP at elevated levels of ICP (table 6.2. While previous experimental work has shown profound Cushing vasopressor responses to extreme and rapid increases in intracranial pressure (figure 6.1)[251,259], in these data we cannot rule out a confounding effect of concurrent interventions and medications such as cooling or vasopressors.

Brain oxygenation

In this sample of patients with extreme increases in ICP, $P_{BT}O_2$ overall decreased. This is consistent with a recent experimental study which demonstrated a cortical vulnerability to increased ICP (chapter 6.1). However, there was marked variation between patients in the levels of $P_{BT}O_2$ and the response to increased ICP (figure A.3). This highlights the complex nature of the $P_{BT}O_2$ variable. It does not merely index brain perfusion, but the complicated interplay between cerebral oxygen delivery (dependent on P_aO_2, Hb, CBF), metabolic rate of the nearby cerebral tissues, and any diffusion barriers[260–262]. Therefore, many clinical scenarios, potentially independent of perfusion, may affect brain oxygenation such as red blood cell transfusion, hypoxia or hyperoxia, mitochondrial dysfunction[163,263]. The position of the oxygen sensing probe may also be relevant as intracontusional oxygen monitoring should be different to pericontusional or healthy tissue monitoring[157]. Furthermore, the

depth of probe may also be relevant; in basilar artery dependent rabbits with CSF infusion induced increases in ICP, the cortical laser Doppler flux was more sensitive to increases in ICP than the global basilar artery flow velocity (chapter 6.1).

Nevertheless, monitoring of brain oxygenation, sometimes in combination with cerebral microdialysis has increased in popularity over last decade with some promising initial results. In a retrospective analysis comparing before $P_{BT}O_2$ to after $P_{BT}O_2$ targeted therapy, found that keeping $P_{BT}O_2$ above 20 mm Hg was associated with decreased mortality[264]. In addition, similar to PRx, brain tissue monitoring has been combined with ABP and CPP monitoring to yield continuous autoregulation assessment in TBI and SAH[118,119,265].

The mean ICP, ICP pulsatile amplitude relationship

The increase in pulsatility of ICP with increasing levels of mean ICP has been interpreted as a loss of cerebral compensatory reserve. In this scenario, when the intracranial system is on the steep ascending portion of the pressure volume curve, a pulsatile injection of blood volume from the cardiac cycle would be expected to produce a large increase in pulsatile pressure. However, at extreme levels of ICP (approaching diastolic blood pressure) it has been demonstrated in animal models that ICP pulsations may in fact decrease (section 6.1 and[266]). This has been proposed to be related to critical closing of the cerebrovascular bed[244]. Observing this phenomenon is however far from universal in refractory intracranial hypertension (figure 6.8), probably as its occurrence is multifactorial, depending on parameters such as vasomotor tone, cerebral intravascular pressures and arterial blood pulse pressure. Interestingly, RAP – the short term correlation between changes in mean ICP and mean amplitude of ICP – did not show a similar upper breakpoint like the pulsatility-mean ICP relationship and rarely reached negative values (figure 6.9 and 6.6) as may have been expected at these extreme levels of ICP[267]. This perhaps reflects the short term dynamic nature of the RAP calculation (calculated over a 5-minute time window) compared with the extended time-windows associated with the pulsatility-mean ICP relationship.

Limitations

Due to the small sample size, these analyses must be considered as preliminary descriptions. While it was possible to include more patients by relaxing the definition of refractory intracranial hypertension we wished to describe the physiological response across the widest range of intracranial pressures and therefore opted to only include patients with severe intracranial hypertension. Further, because intracranial physiology will depend heavily on concurrent therapies, detailed clinical annotations to the monitoring data would aid interpretation. Stratification of physiological responses to intracranial hypertension by ICP treatment modality (for example decompression or barbiturates) may yield useful information describing early indicators of a beneficial vs a pathological physiological response. The

association between early PRx and later development of intracranial hypertension needs to be treated with caution as the case control analysis was only carried out in a small subset of patients with concurrent PRx monitoring (n=24). Furthermore, time-points besides the first 4 hours for the ability of PRx to predict intracranial hypertension should be investigated. While ongoing data collection with the increasing availability of multimodality monitoring will likely shed light on this area in the near future, controlled experimental studies that mimic the increase in ICP observed after human TBI need to also play a role as they can effectively isolate the effects of the disease from that of treatment.

Conclusion

Severe intracranial hypertension after traumatic brain injury leads to decreased brain oxygenation, impaired pressure reactivity and a characteristic ICP pulsatility response.

Chapter 7

Novel applications of intracranial monitoring after severe traumatic brain injury

Results on which this chapter is based:

- Donnelly, J., Czosnyka, M., Adams, H., Robba, C., Steiner, L.A., Cardim, D., Cabella, B., Liu, X., Ercole, A., Hutchinson, P.J. and Menon, D.K., Aries, M.J., Smielewski, P. 2017. Individualizing Thresholds of Cerebral Perfusion Pressure Using Estimated Limits of Autoregulation. Critical Care Medicine, 45(9), pp.1464-1471.

7.1 Individualising thresholds of cerebral perfusion pressure using estimated limits of autoregulation

7.1.1 Introduction

After the initial trauma, secondary insults such as cerebral ischaemia contribute to poor outcome and their early detection and amelioration are central to neurocritical care[268]. Maintaining cerebral perfusion pressure above a certain limit may help decrease cerebral ischaemia but a CPP that is driven too high may contribute to cerebral oedema or precipitate systemic complications[269]. On this basis, current Brain Trauma Foundation (BTF) guidelines recommend maintaining CPP between 60 and 70 mm Hg[134].

The cerebrovascular pressure reactivity index has been proposed as a guide for individualizing CPP management[80]. In this autoregulation based technique, PRx is plotted against trends in CPP to create a U-shaped CPP-PRx curve outlining the CPP at which pressure reactivity is more efficient - the CPPopt (figure 7.1)[80,81]. This procedure is applied iteratively on moving calculations on recent patients' data to provide (semi) continuous CPP-PRx curves and CPP targets. Data supporting the utility of this approach, despite deriving from a relatively small number of retrospective analyses, are promising[81,179,180,270,271].

However, existing studies have focused on identifying one autoregulation guided CPP target ignoring the fact that a broader CPP range might provide similar autoregulation benefit. As depicted on figure 7.1, understanding the position and shape of CPP-PRx may help us identify the CPP below which PRx is impaired (the Lower Limit of Reactivity; LLR), the CPP above which PRx is again impaired (Upper Limit of Reactivity; ULR) and the CPP range associated with intact PRx (within limits of reactivity; WLR).

Our aim was to extend our current individualised CPP recommendation method to determine continuously and automatically the CPP range with intact pressure reactivity in a single centre dataset of severe TBI patients (1996-2016). We compared the performance of these dynamic individual CPP autoregulation thresholds, with the CPPopt target and the recommended fixed CPP thresholds by evaluating the relationships with outcome.
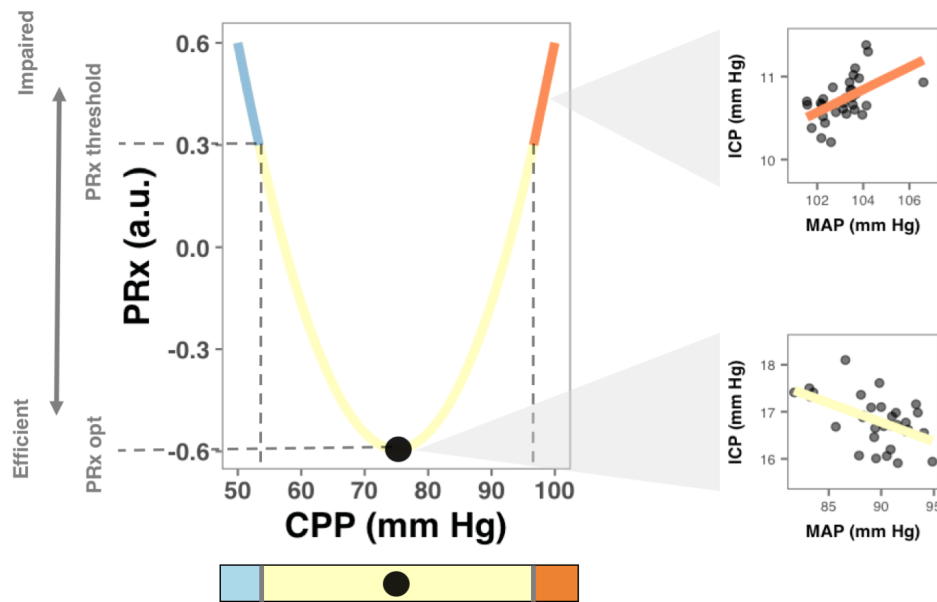
Figure 7.1: **Schematic depicting the theoretical relationships between CPP and PRx including estimation of CPPopt, CPP LLR, and CPP ULR.** The relationship between CPP and PRx can be approximated by fitting a U-shaped curve (2nd order polynomial) whereby with both high or low values of CPP, the cerebral pressure reactivity (PRx) is impaired (top right panel). With impaired PRx there is a positive correlation between changes in MAP and changes in ICP (normally calculated over a 5-minute window) However, for intermediate CPP values, PRx is (probably) efficient (bottom right panel), and the CPP at which PRx is most negative is termed the CPPopt (as indicated by the black dot). By applying a threshold for impaired cerebral PRx, the CPP at which PRx switches from being intact to impaired can be calculated to give an estimate of the lower and upper CPP limits of reactivity (LLR and ULR respectively). By summarising the relationships between CPP and the various parameters (LLR, ULR, CPPopt), we can appreciate how far a patients CPP is from their autoregulation guided target or range.*CPP* cerebral perfusion pressure; *PRx* pressure reactivity index; *MAP* mean arterial pressure; *ICP* intracranial pressure; *CPPopt* cerebral perfusion pressure optimal; *PRxopt* pressure reactivity optimal; *ULR* upper limit of reactivity; *LLR* lower limit of reactivity.

7.1.2 Methods

Patients

836 severe TBI patients entering the neurocritical care unit (NCCU) with computerized ICP monitoring (September 1996 - June 2016) were selected. 107 patients were removed (<12 hours (ICP) monitoring data, age <=12 years old, no PRx available, Glasgow

Outcome Score (GOS) not available), leaving 748 patients for final analysis. Pupil reactivity information was only available in 207 (28%) of patients. Use of computer-recorded data was approved by NCCU Users' Committee and conducted before 2000 as a part of anonymous clinical audit. After 2000, regional ethical approval was obtained (30 REC 97/291) for anonymized data recording. Patients were managed according to TBI guidelines[14] aimed at keeping ICP < 20 mm Hg and CPP > 50-60 mm Hg. CPPopt or PRx-guided management was not part of the management algorithm. GOS was obtained at 6 months by outpatient assessment[272].

Data Acquisition and Processing

ICP was monitored with an intraparenchymal sensor (Codman ICP Micro- Sensor, Codman & Shurtleff, Raynham, MA). ABP was zeroed at the level of the right atrium from 1996 to March 2015, and at the level of the external acoustic meatus thereafter (Baxter Health- care CA, USA; Sidcup, UK). No corrections were made for hydrostatic pressure influence. Data were sampled at 100 Hz with proprietary data acquisition and analysis software (ICM+©, `http://www.neurosurg.cam.ac.uk/icmplus`). PRx was calculated as described in section 2

Automated CPP-PRx curve fitting and CPPopt determination

CPP-PRx curve fitting was calculated as described previously[81]. Briefly, 5-minute periods of mean CPP (updated every minute) were collected alongside 1-minute mean values of PRx. These PRx values were then binned into 5 mm Hg-wide CPP intervals. These data were plotted as an error bar chart with CPP on the x-axis and PRx on the y-axis. A second order polynomial curve was fitted after 4-hours of data collection with predefined heuristics and the resulting local minimum was denoted CPPopt (figure 7.1). A moving window with one-minute updates was used to generate a trend of CPPopt.

To address the issue of a relatively low yield of CPPopt curves introduced by the strict physiologic heuristic constraints of the curve fitting process[81], we used the averaging method proposed by Depreitere et al.[270] Instead of a single-calculation window (of 4-hours) to produce the CPP-PRx curve parameters (CPPopt, LLR, ULR, WLR), multiple calculation windows were applied from a period of 2 hours to 8 hours (in 10-minute increments) to yield up to 36 estimations. The mean of these estimates was calculated and updated every minute[273].

ΔCPPopt was calculated as the patients' CPP minus the calculated (multi-window) CPPopt every minute. Positive and negative values were interpreted as the time a patient spent (%) with a CPP above or below the CPPopt, respectively. ΔCPPopt is independent of the level of head elevation and therefore possible errors derived from hydrostatic influences are compensated for.

Automated estimation of the lower and upper CPP limits of reactivity

The defined CPP-PRx curve was extrapolated to both sides to include the full range of plausible CPP values (from 40 -120 mm Hg) to obtain the CPP values at which the curve crossed the threshold PRx value for impaired pressure reactivity (PRx= +0.25). The value of CPP at these two points of intersection were denoted automatically the LLR and ULR, respectively. If a curve was entirely above the PRx threshold, no intersection could be calculated and thus the LLR and ULR were set to equal the CPPopt. In addition, extreme values for the estimated LLR and ULR (less than 40, and 120 mm Hg) were defaulted to 40 or 120 mm Hg, respectively. Furthermore, where the fitted CPP-PRx yielded a monotonically ascending or descending curve with no inflection point, no strict intersection with the PRx threshold could be calculated and thus the LLR was taken to be 40 mm Hg, and the ULR 120 mm Hg, respectively. For example, if a descending curve (no inflection point), crossed the threshold at a CPP of 50 mm Hg, the LLR would be denoted 50 mm Hg, and the ULR would default to 120 mm Hg. The value of 0.25 as a threshold for PRx was chosen as it has been identified as a critical threshold for determining fatal outcome in a previous study of severe TBI patients in our cohort[136].

Statistical analysis

We compared the fixed CPP thresholds with the two flexible autoregulation guided thresholds:

1. guideline CPP thresholds (lower = 60; upper = 70 mm Hg);

2. the CPPopt-based thresholds (lower= a CPP more than 10 mm Hg below CPPopt or ΔCPPopt < -10; upper= a CPP more than 10 mm Hg above CPPopt or ΔCPPopt > +10);

3. the flexible CPP reactivity thresholds (lower= LLR; upper= ULR).

For each patient, the amount of time (%) spent below the lower threshold, above the upper threshold, and between both thresholds was calculated and then compared across dichotomised outcome groups. Unfavourable outcome was defined as death, vegetative state or severe disability. Univariate outcome relationships were performed by comparing Receiver Operating Curves (ROC) attributes. For each CPP threshold approach multivariable logistic regression models were constructed for outcome prediction. Available covariates in our 1996-2016 cohort were age, GCS and mean ICP. The best subset selection algorithm was applied using an exhaustive method that searches the best model, based on the lowest Akaike Information Criterion (AIC)[274]. We used the R language and software environment for statistical computation[154] using the following packages: dplyr[149], ggplot2[150], bestglm[148]. The significance level was set at 0.05.

7.1.3   Results

Patient characteristics

Of the 748 patients, one patient did not have any valid CPPopt curve availiability, leaving 747 for the analysis. This patient did not have CPP values above 30 mm Hg. Summary data are shown in table 7.1. The mean age was 39.1 (16.93). Mean ICP was 15.01 (6.16) mm Hg and mean CPP was 78.57 (7.66) mm Hg. The mean CPPopt was 77.4 (7.06) mm Hg and compared with the single 4-hour window, the CPPopt availability (calculated from the time of first estimate) increased significantly with the multi-window approach (59.71 $\pm$ 13.98 % vs. 92.84 $\pm$ 8.86 of the monitoring period, p<0.001).

The CPP limits of cerebrovascular reactivity

The mean CPP LLR and ULR for the cohort were 59.37 ($\pm$ 7.44) mm Hg and 95.53 ($\pm$ 7.57) mm Hg while the mean WLR was 36.16 ($\pm$ 8.37) mm Hg. Two patient examples of the interaction between CPP, and the CPP LLR and ULR are shown in figure 7.2. The interrelationships between flexible CPP thresholds and other physiologic variables are depicted in a correlation matrix (figure 7.3). Notably, the WLR was significantly related to mean PRx (r=-0.78, p <0.001). Older patients tended to have a smaller WLR range and a higher CPP LLR which might indicate a rightward shifted and narrower autoregulation plateau.

Table 7.1: Patient demographics; individualised CPP thresholds after TBI

	Overall
n	747
GOS (%)	
D	159 (21.3)
VS	13 (1.7)
SD	246 (32.9)
MD	185 (24.8)
GR	144 (19.3)
Age [years] (mean (sd))	39.06 (16.91)
Sex = male (%)	589 (78.8)
GCS <= 8 = TRUE (%)	548 (73.4)
Decompressive craniectomy (%)	
FALSE	416 (55.7)
TRUE	165 (22.1)
NA	166 (22.2)
Monitoring length (hours) (mean (sd))	138.40 (105.94)
ICP [mm Hg] (mean (sd))	14.94 (5.88)

	Overall
CPP [mm Hg] (mean (sd))	78.65 (7.37)
PRx [a.u.] (mean (sd))	0.06 (0.16)
Multi-window yield [%] (mean (sd))	92.96 (8.18)
Single-window yield [%] (mean (sd))	59.79 (13.81)
LLR [mm Hg] (mean (sd))	59.37 (7.44)
ULR [mm Hg] (mean (sd))	95.53 (7.57)
WLR [mm Hg] (mean (sd))	36.16 (8.37)
CPP < LLR [%] (mean (sd))	10.47 (13.65)
CPP > ULR [%] (mean (sd))	12.96 (11.34)
CPP WLR [%] (mean (sd))	76.57 (18.77)
CPP < 60 [%] (mean (sd))	5.18 (9.11)
CPP 60-70 [%] (mean (sd))	19.31 (13.07)
CPP > 70 [%] (mean (sd))	75.51 (18.51)
ΔCPPopt < -10 [%] (mean (sd))	17.10 (11.57)
ΔCPPopt ± 10 [%] (mean (sd))	59.35 (11.73)
ΔCPPopt > +10 [%] (mean (sd))	23.55 (12.48)

GOS Glasgow oucome scale; *D* death; *VS* vegetative state; *SD* severe disability; *MD* moderate disability; *GR* good recovery; *GCS* Glasgow coma scale; *ICP* intracranial pressure; *CPP* cerebral perfusion pressure; *PRx* pressure reactivity index; *opt* optimal; *ULR* upper limit of reactivity; *LLR* lower limit of reactivity; Δ*CPPopt* cerebral perfusion pressure minus cerebral perfusion pressure optimal.

Figure 7.2: **Continuous estimation of CPP LLR and ULR in a patient with good recovery (A), and death (B) after severe TBI.** Based on a previously described visualisation approach[275], the orange area represents CPP values that were above CPP ULR, blue area represents CPP values below the CPP LLR and the yellow area CPP values that are WLR. The black line represents the patients' instantaneous value of CPP. It can be appreciated that these CPP limits of reactivity are not fixed, but change across the different patients and also over time within each patient. In the patient who died (B) especially during the first two days of monitoring the CPP LLR was high, the CPP ULR was lower and thus WLR was smaller or absent. This patient spent significant amounts of time with CPP below the LLR, whereas in the patient that had good recovery, the majority of time the CPP was between the LLR and ULR. *CPP* cerebral perfusion pressure; *LLR* lower limit of reactivity; *ULR* upper limit of reactivity; *WLR* within cerebral perfusion pressure limits of reactivity.
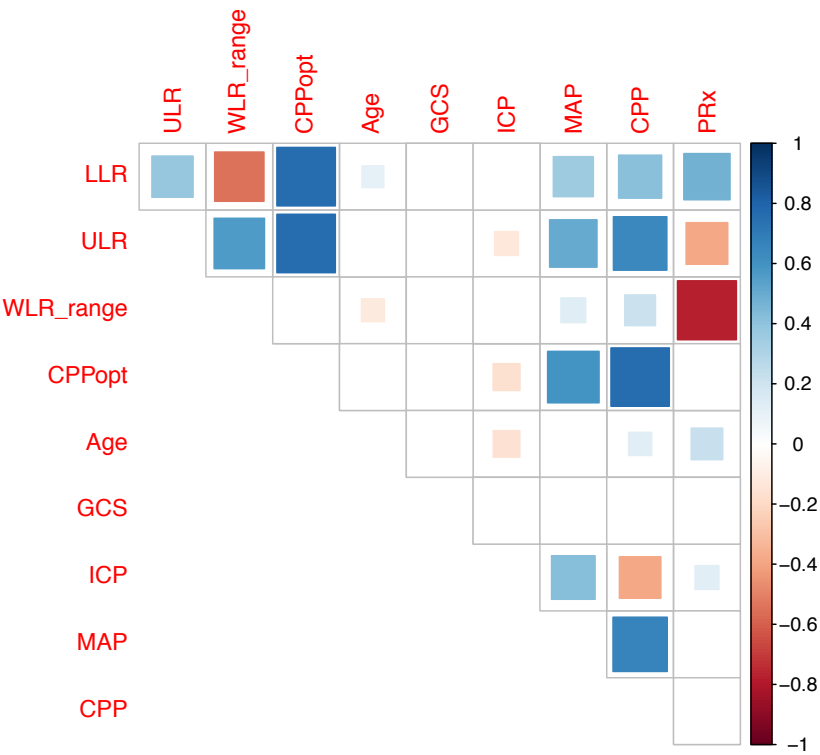
Figure 7.3: **Correlation matrix of the relationship between limits of reactivity and other physiologic values after severe TBI.** The strength of each (Pearson) correlation is denoted by the colour and the size of the square. Only significant correlations are shown (at the level of p<0.005). *ICP* intracranial pressure; *CPP* cerebral perfusion pressure; *MAP* mean arterial pressure; *PRx* pressure reactivity index; *LLR* lower limit of reactivity; *ULR* upper limit of reactivity; *WLR* within cerebral perfusion pressure limits of reactivity; $\Delta CPPopt$ cerebral perfusion pressure minus cerebral perfusion pressure optimal; *GCS* – Glasgow coma scale.

Prognostic significance of CPP: fixed vs flexible CPP thresholds

Spending more time with CPP < 60 was related to death (figure 7.4), whereas spending more time with CPP > 70 was not (in fact inversely related). These findings were confirmed in AUC analysis (figure 7.5, appendix A - table A.2). In all outcome groups, the % of time within the guideline CPP range was low (figure 7.4, mean 19.29 ($\pm$ 13.08)%.

Time with ΔCPPopt < -10 was significantly related to mortality, whereas spending more time with ΔCPPopt > +10 was not (similar to CPP > 70, there was an inverse relationship) (figure 7.4, table A.2). The % of time with CPP < LLR was a significant predictor of both unfavourable outcome and mortality and the % of time with CPP > ULR predicted unfavourable outcome but not mortality (appendix A, table A.2).

For all three approaches, looking at absolute time (rather than % time as described here) gives quantitatively similar results (data not shown).

Based on the univariate analyses, % time with CPP below each threshold was included in initial models predicting mortality, whereas % time with CPP above and below each threshold were included in the initial models predicting unfavourable outcome. After applying the best subset algorithm, % time with CPP above the upper thresholds were not present in any model. Multivariate models using the flexible CPP reactivity limits (rather than fixed CPP or ΔCPPopt limits) showed the best ability to predict unfavourable outcome (AUROC=0.75) and mortality (AUROC=0.82) (appendix A, table A.3).
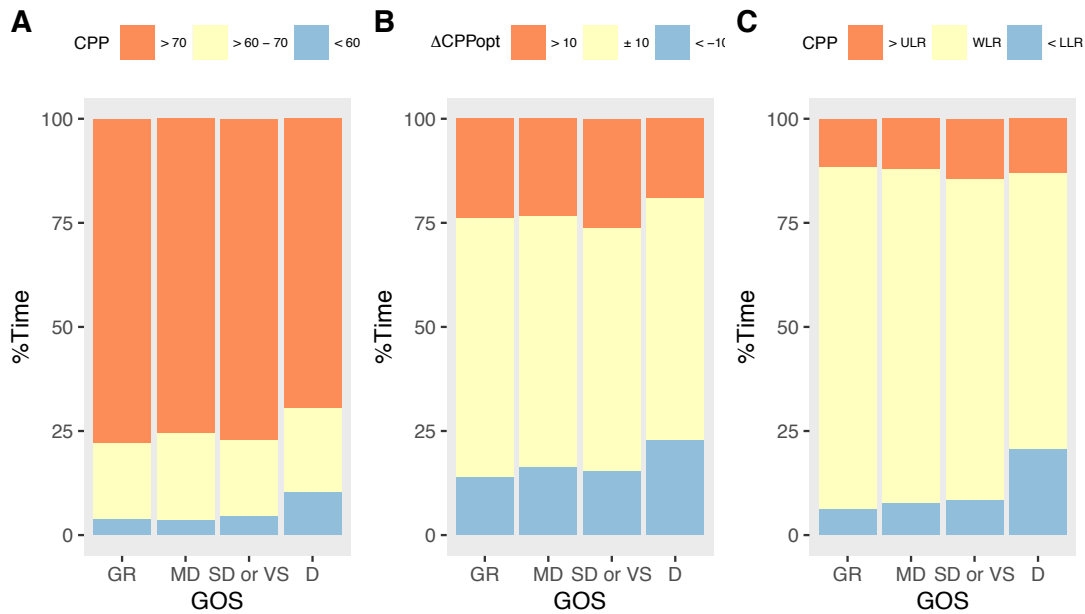
Figure 7.4: **Comparison of %time spent in different 'zones' of CPP as defined by fixed thresholds (left), CPPopt based thresholds (middle), or flexible limits of reactivity (right).** A. Using the BTF recommended fixed CPP values of 60 and 70 mm Hg as lower and upper thresholds, most patients spent the majority of time with a CPP above the upper threshold. In those that died, the proportion of time with CPP > 70 mm Hg was lowest, and proportion of time with CPP < 60 mm Hg the highest. B. The CPPopt-based thresholds were estimated as follows: lower threshold was a CPP more than 10 mm Hg below CPPopt (ΔCPPopt < -10); while the upper threshold was a CPP more than 10 mm Hg above CPPopt (ΔCPPopt > +10). Those with severe disability or vegetative state spent the most amount of time above the upper CPPopt threshold, while those who died spent the most time with CPP below the lower CPPopt threshold. C. Referencing patients current CPP to their individually estimated lower and upper limits of reactivity (LLR and ULR respectively) reveals the most consistent pattern; those patients with increasing burden of disability spent more time with a CPP below their LLR and above their ULR. *GOS* Glasgow oucome scale; *D* death; *VS* vegetative state; *SD* severe disability; *MD* moderate disability; *GR* good recovery; *CPP* cerebral perfusion pressure; *CPPopt* cerebral perfusion pressure optimal; *LLR* lower limit of reactivity; Δ*CPPopt* cerebral perfusion pressure minus cerebral perfusion pressure optimal; *BTF* Brain Trauma Foundation.
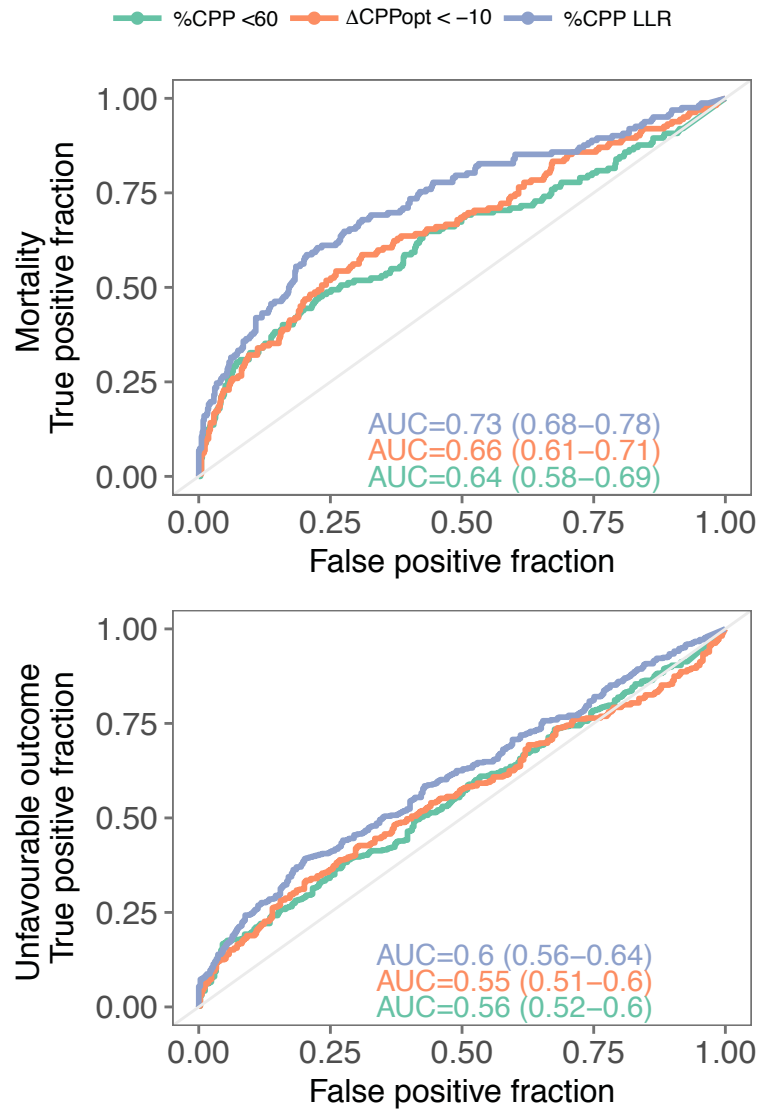
Figure 7.5: **Comparison of receiver operator characteristic (ROC) curves for predicting mortality (top) and unfavourable outcome (bottom).** Percentage of time with CPP below the lower limit of reactivity (%CPP less than LLR) was the strongest predictor of mortality and unfavourable outcome. *CPP* cerebral perfusion pressure; $\Delta CPPopt$ cerebral perfusion pressure minus cerebral perfusion pressure optimal; *LLR* lower limit of reactivity; *ULR* upper limit of reactivity; *AUC* area under the (receiver operating) curve.

Table 7.2: Multivariable outcome analysis for mortality; individualised CPP thresholds after TBI

Statistic	% CPP<LLR	p	%ΔCPPopt <-10	p	%CPP <60	p
% CPP < LLR (OR)	1.06 (1.04-1.08)	<0.001				
% ΔCPPopt < -10 (OR)			1.04 (1.03-1.06)	<0.001		
% CPP<60 (OR)					1.04 (1.02-1.06)	<0.001
ICP (mm Hg) (OR)	1.12 (1.08-1.16)	<0.001	1.12 (1.08-1.16)	<0.001	1.1 (1.06-1.15)	<0.001
Intercept (OR)	0.01 (0-0.03)	<0.001	0.01 (0-0.03)	<0.001	0.02 (0.01-0.05)	<0.001
Age (OR)	1.05 (1.03-1.06)	<0.001	1.05 (1.03-1.06)	<0.001	1.05 (1.03-1.06)	<0.001
GCS (OR)	0.87 (0.81-0.92)	<0.001	0.85 (0.79-0.91)	<0.001	0.86 (0.81-0.92)	<0.001
AIC	601.39		633.14		656.99	
Log-Likelihood ratio	-295.7		-311.57		-323.49	
AUC	0.82		0.79		0.78	

CPP cerebral pefusion pressure; *OR* odds ratio; *ICP* intracranial pressure; *ΔCPPopt* cerebral perfusion pressure minus cerebral perfusion pressure optimal; *LLR* lower limit of reactivity; *GCS* Glasgow coma scale; *AIC* Akaike information criteria; *AUC* area under the (receiver operating characteristic) curve.

7.1.4   Discussion

In this study of 748 severe TBI patients, we extended our autoregulation guided CPP method with a novel technique that in addition to the CPPopt value, also estimates the CPP limits of cerebral pressure reactivity. We demonstrated that deviation of CPP from the autoregulation guided individual and flexible thresholds is related to patient outcome, even after adjusting for important TBI prognostic covariates.

Characterizing CPP limits of pressure reactivity using the CPP-PRx curve

Similar to the recently developed visualisation method of the CPP-PRx landscape[275], the continuous estimation of CPP LLR and ULR provides the clinician with more contextual information to the single CPPopt value and therefore may align better with clinical acumen. While targeting the CPPopt is a practical option for a randomized clinical trial, there are clinical situations where strictly targeting the CPPopt continuously might be risky and may outweigh the overall potential benefit. For example, in a patient with a broad CPP pressure reactivity range lower CPP targets can be accepted for a certain period limiting the need for administration of large doses of potentially damaging vasopressors and fluids[140]. In this scenario, management based on the individual autoregulation-guided CPP could be a compromise between the aggressive CPP oriented therapy promulgated by Rosner et al. and the more permissive Lund protocol[139,276].

The CPP-PRx curve- a pragmatic and prognostically important relationship

The time spent with CPP < LLR and (10 mm Hg) deviation below CPPopt were significantly related to adverse outcome (tables A.2, A.3, figure 7.4, 7.5), fitting with the clinical maxim that periods with low CPP should be avoided in severe TBI patients[81,134,277]. There is evidence that even short periods of cerebral hypoperfusion contribute to secondary brain injury and are related to unfavourable outcome[277]. Indeed, a large body of evidence indicates that a low CPP is deleterious through a range of interrelated pathways including deranged cortical and global cerebral blood flow, oxygenation, and metabolism[172,278]. The sequelae of having a CPP > ULR and (10 mm Hg) deviation above CPPopt are less clear; in this large cohort, only modest relationship to unfavourable outcome was found (table A.2, figure 7.4). While this could perhaps indicate that the morbidity caused by periods of 'hyperperfusion' is outweighed by the morbidity engendered by periods of 'hypoperfusion', it is also possible that deleterious effects of aggressively elevated CPP are not detected by our coarse outcome measures (GOS).

   The observation that PRx was strongly positively related to LLR and negatively related to the WLR (figure 7.3), has pragmatic implications: the complex concept of PRx can be translated into something immediately clinically meaningful- a number that represents margins of individual cerebral autoregulatory capacity. This idea fits with the current guidelines stating that higher and lower CPP values might be accepted dependent on

autoregulation status[134].

It is notable that when time spent with CPP < LLR is grouped by patient outcome, the major differences are between those that died and survived, rather than distinguishing between the individual categories of survival (GOS 2-5). A similar phenomenon was found with TBI prognostic models applied to the large CRASH database[146,229], highlighting the urgent need for further investigation into novel TBI prognostic markers. It is also striking that most patients spent significant periods of time with CPP above current recommendations (table 7.1, figure 7.4). Similar observations can be found in other recent studies[182,264,279].

Limitations

This study has several important limitations. By nature of its observational design, conclusions about whether an autoregulation-guided CPP protocol will improve patient physiology or outcome are not possible. Nevertheless, the extension of the method described here seems crucial for the design of different prospective trials. Practical and safety issues might guide choices between strict flexible targets, flexible thresholds or even flexible ranges.

The algorithm for the CPP-PRx curve fitting and deriving the CPPopt and limits of reactivity as described here represents current efforts but does not preclude modifications or alternative strategies. Specifically, modelling the CPP-PRx relationship using a 2nd order polynomial may be an oversimplification, as may applying the same heuristic constraints to the LLR and ULR estimation as to CPPopt. This is particularly pertinent to the estimation of the ULR, because while the curve fitting procedure demands a symmetrical 'u-shape' relationship between CPP and PRx, it may be that CPP levels above a CPPopt are not as deleterious to PRx as CPP levels of equivalent magnitude below the CPPopt (i.e., the 'u-shape' may not be symmetrical). Unlike the case for the LLR, whether PRx can reliably indicate the ULR has not been determined and should be the focus of further experimental and clinical research efforts. Further, factors other than ICP/CPP may also affect pressure reactivity or autoregulation[49,162,163,182]—like CO_2 levels—and are not currently considered in the current concept and related management. However, the analysis of multimodal data (like in the high resolution CENTER-TBI study; `https://www.center-tbi.eu`) might give insights in the near future[280].

Given that the monitoring data (including the single window CPP-PRx curve) was not hidden from the treating clinicians, it is possible that in some cases, patient management decisions could have been influenced by the clinician evaluating the CPP-PRx relationship, despite this not being in the treatment protocol during the 1996-2016 period. Unfortunately, we do not have information on whether this was the case, and if so, the potential magnitude of the effect.

Finally, a detailed analysis of the effect of various clinical scenarios on the CPP-PRx relationship was not addressed in the current study including the influence of decompressive

craniectomies, the influence of a more complete initial injury severity descriptors (i.e., extracranial injury, pupil reactivity) or the specific type of TBI pathology, or indeed the time-course of the studied physiological relationships. These should be explored in future studies. In spite of these caveats, CPPopt deviation and CPP LLR threshold have been shown to be prognostically relevant in a large cohort of 747 patients.

Conclusion

By examination of the CPP-PRx relationship we can not only estimate the CPPopt but also derive a continuous estimation of the lower and upper CPP limits of PRx. Deviation of CPP from autoregulation-guided flexible thresholds is related to patient outcome. Prospective randomized research is needed to define which autoregulation guided method is most beneficial, safe and practical.

7.2 Visualisation of ICP insults after severe TBI; influence of individualised limits of reactivity

7.2.1 Introduction

Lower and upper CPP limits of reactivity can be determined almost continuously (section 7.1), and deviation below the lower limit carries important prognostic information (appendix A, table A.3). Therefore, knowledge of an individualised CPP LLR could potentially indicate to the treating clinician whether a given CPP or ICP is likely to be detrimental or beneficial to the patient. However, whether having a CPP above the lower limit of reactivity actually renders the patient protected from high ICP (or low CPP) has not been explored.

In this study, we use a recently derived method for visualising ICP and CPP insults to describe the effect of having a CPP within the CPP limits of reactivity. Given that previous investigations have shown a protective effect of intact cerebrovascular pressure reactivity[137] and the LLR was strongly correlated with PRx (figure 7.3), we hypothesise that ICP insults with a CPP above the LLR will not be as harmul as similar ICP insults with CPP below the LLR.

7.2.2 Methods

Patients and data acquisition

The same cohort of (747) severe TBI patients, and the same data aquisition procedures were used as in section 7.1. Minute-by-minute values of CPP, ICP, and the CPP LLR were used for further processing.

ICP visualisation

A procedure has previously been described for visualising the how ICP insult characteristics (magnitude and duration) relate to patient outcome[137]. This procedure involves segmenting ICP time-series into 'ICP insults' and then relating the number of insults (with particular intensity-duration characteristics) with patient outcome at 6-months.

For each patient, the ICP time-series was segmented into episodes above a particular threshold (starting with 10 mm Hg). For each episode the duration above the threshold as well as the mean difference between CPP and the LLR were calculated. This process was repeated for thresholds of 11 to 40 mm Hg. The resulting ICP 'episodes' were collated for every patient. A new row of data was created for each minute the episode was greater than the ICP threshold (from 5 minutes) until the total duration of the episode was reached. For example, an episode of >25 mm Hg for 7 minutes, was described as an episode greater than 25 mm Hg for at least 7 minutes, an episode of at least 6 minutes, and an episode of at least 5 minutes. Thus a matrix was created that listed ICP episodes of at least (10-40

mm Hg) for at least (5-360 minutes). For each ICP insults, the difference between CPP and LLR was calculated and dichotomised as CPP being above or below LLR.

To replicate the method as previously published[137,165], the Pearson correlation was calculated between the mean number of episodes per patient and GOS (used in an ordinal scale 1=death, 2= vegetative state, 3 = severe disability, 4 = moderate disability, 5= good recovery) for each minimum duration (5-360 minutes) and intensity (10-40 mm Hg) of ICP insult. This was then displayed as a coloured contour plot with a negative correlation (shown in red) between GOS and number of episodes implying that those characteristics (duration and magnitude) are harmful and a positive correlation (shown in blue) indicating those particular characteristics were associated with better outcomes. The contour between a positive and a negative correlation (R=0) was used as a landmark 'transition zone'[137]. For each patient, the percentage of time was calculated that the patient spent with insults more intense, or lasting longer than the transition zone characteristics.

Statistical analysis

Multivariable generalised linear models were used to assess the influence of time in the ICP red-zone and mortality or unfavourable outcome. We used the R language and software environment for statistical computation (R Core Team 2015 version 2.12.1) using the following packages: dplyr[149], and ggplot2[150]. The significance level was set at 0.05.

7.2.3   Results

A description of demographic characteristics of the patient cohort are displayed in table 7.1.

Figure 7.6 demonstrates how the duration and intensity of ICP insults can interact to have detrimental effects on GOS. Short periods (~5 minutes) of ICP greater than 25 mm Hg have similar effects on patient outcome as ~50 minutes of ICP greater than 20 mm Hg or ~4 hours ICP >15 mm Hg. On multivariable analysis, after adjusting for GCS and age, the time spent in the dangerous zone (defined here as a more intense, or longer insult than the transition zone) was associated with unfavourable outcome and mortality (table 7.3).

The modification of this relationship by the individualised lower limit of CPP is demonstrated in figure 7.7A. When CPP was below the LLR, (2 million episodes), even short and mild ICP insults were detrimental whereas when CPP was above the LLR, similarly short and mild insults were not associated with poor outcome (figure 7.7B).
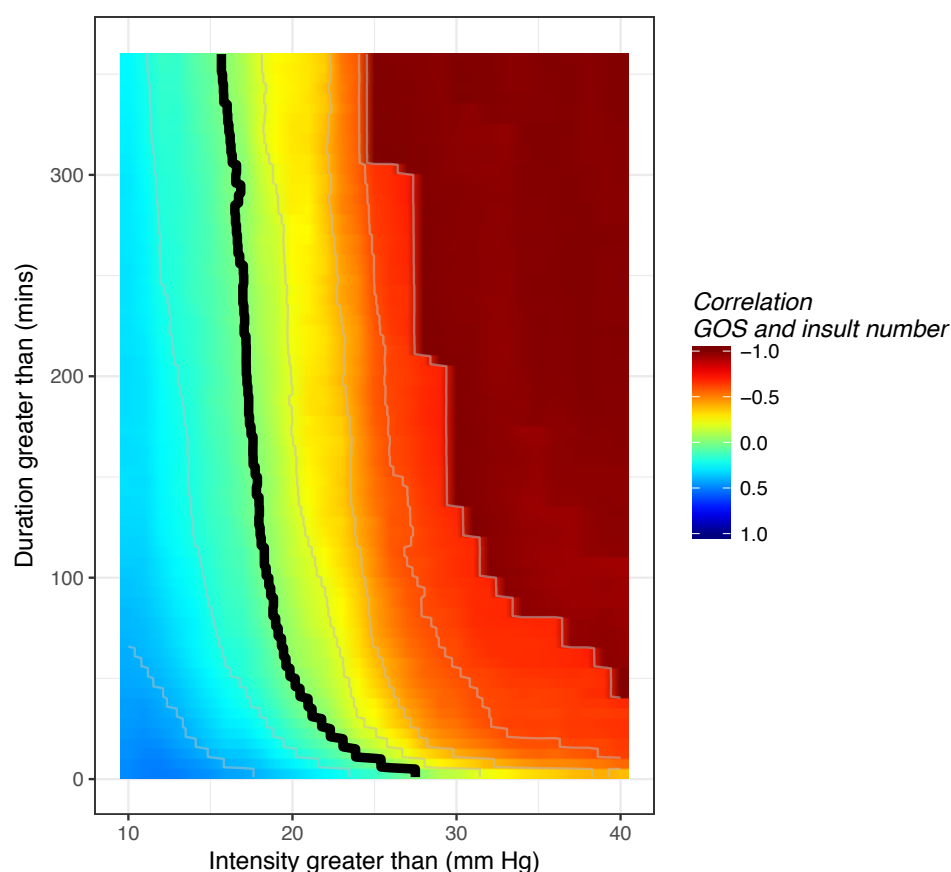
Figure 7.6: **Visualisation of relationship between number of ICP insults (of a particular duration and intensity) and GOS after severe TBI (747 patients, 24 million insults).** The transition zone (black) is depicted as a curvilinear function indicating that higher intensity ICP insults can be tolerated for a short period of time without beaing associated with poorer outcome. Above 30 mm Hg almost any duration of insult is strongly correlated with GOS (< -0.5). *GOS* Glasgow outcome scale; *ICP* intracranial pressure.

Table 7.3: Multivariable outcome analysis for mortality and unfavourable outcome; individualised CPP thresholds after TBI

Statistic	Mortality	p	Unfavourable outcome	p
% time in red-zone	1.03 (1.03-1.04)	<0.001	1.02 (1.01-1.03)	<0.001
(Intercept)	0.07 (0.04-0.13)	<0.001	0.94 (0.58-1.52)	0.802
Age	1.05 (1.03-1.06)	<0.001	1.04 (1.03-1.05)	<0.001
Initial GCS	0.85 (0.8-0.9)	<0.001	0.81 (0.77-0.85)	<0.001
AIC	732.93		995.5	
logLik	-362.47		-493.75	
AUC	0.78		0.75	

GCS Glasgow coma scale; *AIC* Akaike information criteria; *AUC* area under the (receiver operating characteristic) curve; *logLik* log likelihood.
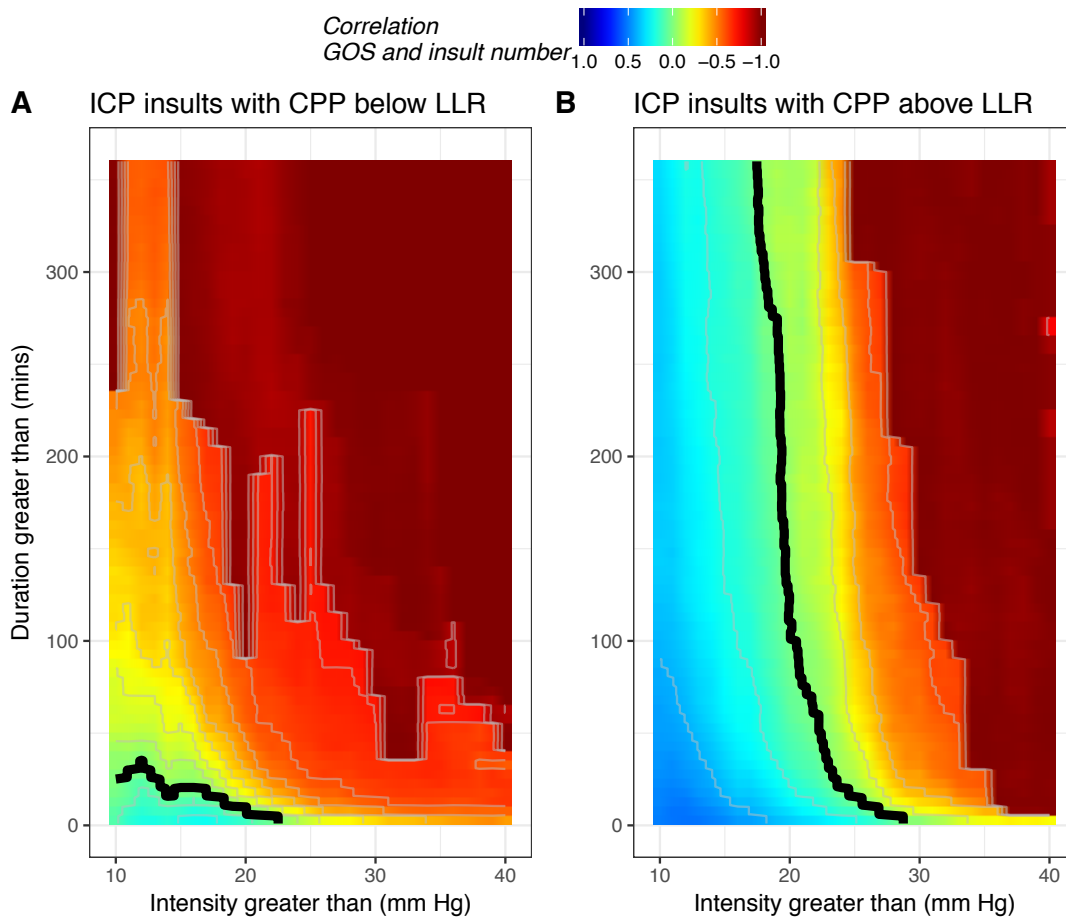
Figure 7.7: **Visualisation of relationship between number of ICP insults (of a particular duration and intensity) and GOS after severe TBI when CPP is below the LLR (A, 2 million insults) or above the LLR (B. 21 million insults).** When CPP is below the LLR during an insult, even low intensity ICP insults are associated with worse GOS as denoted by the predominance of red in A. This contrasts to ICP insults when CPP is above the LLR - in this case the transition zone is shifted rightward indicating a degree of protection. *ICP* intracranial pressure; *LLR* lower limit of reactivity; *GOS* Glasgow outcome scale.

7.2.4 Discussion

The individualised CPP lower limit of reactivity significantly modify the relationship of ICP insults with patient outcome. A CPP within the limits of reactivity exerts a protective effect while a CPP outside the reactivity limits renders the patient vulnerable to increased morbidity.

Visualisation

With the wealth of physiological information now available at the bedside of TBI patients (microdialysis, $P_{BT}O_2$, ICP, CBF, Near infrared spectroscopy), the effective presentation of the most clinically relevant data is of paramount importance[281]. While previously,

physiological derangements after TBI were associated with patient outcome based on the crude univariate relationship between the mean value of the signal and patient outcome, recent advances have allowed us to consider individual physiological insults in terms of two key factors – intensity and duration[137,165,282,283]. This distinction is critically important because decisions in the intensive care environment need to be made on the basis of available evidence about the current insult, not on aggregate data of whole monitoring period averages.

Contour lines on the plots represent insult characteristics (intensity and duration) that are associated with the same level of harm (correlation between number of insults and GOS). In this way, the interplay between duration and intensity can be easily appreciated; while short insults can be tolerated without increasing morbidity, longer insults are associated with a higher proportion of adverse outcomes. Whilst thus far applied to ICP and CPP insults, similar methods could easily be applied to any monitoring modality. A useful feature of such intensity-duration plots is that thresholds of a 'dangerous ICP' are can be defined with a consideration of duration and intensity for example, an ICP 25 mm Hg can be tolerated for 5 minutes but not 20 minutes (figure 7.6). This contrast with the approach previously used by Sorrentino et al where thresholds for monitored variables (ICP, CPP, PRx) were derived from the statistical association with outcome for patient averaged values over the whole monitoring period[136]. Whether such derived thresholds should be applied without consideration of duration has not been studied.

Individual limits

The goal of precision medicine is to improve patient outcomes by tailoring therapy to the individual patient[284]. Potential avenues for precision medicine in the critical care environment include the personalisation of targets for monitored variables. Preliminary efforts in traumatic brain injury have focused on indivisualsing cerebral perfusion pressure targets based on a metric of cerebral vascular function[80,81,256,273] and have yielded promising results in retrospective analysis. Here we show that having a CPP within the limits of reactivity affords significant protection from ICP insults (figure 7.7); for the same intensity and duration of ICP insult, the correlation of number of insults with poor outcome is lower if CPP is above the LLR.

Limitations

Several important limitations need to be discussed. First, the influence of harm from CPP or ICP therapy cannot be dissociated from harm from the CPP or ICP alone i.e. it is possible that some of the morbidity associated with an episode of ICP above 30 mm Hg may be attributable to the use of large doses of vasopressors or ICP lowering therapies like barbiturate coma.

Second, detailed analysis of admission characteristics (initial CT scan findings, ex-tracranial injury severity, co-morbid conditions) are not available in this retrospective

database which could lead to a more accurate prognostic model. Third, this analysis includes patients with decompressive craniectomies, which may influence how ICP insults are tolerated. A further analysis in those with and without decompressions is warranted. Finally, using PRx to estimate CPP lower and upper thresholds represent just one approach and other indicators such as phase shift between ABP and ICP, a low frequency correlation coefficient between ABP and ICP and NIRS based methods could also be used but have not been examined here.

Conclusions

A CPP above the lower limit reactivity protects the brain from ICP insults. Prospective evaluation of insult visualisation and automated CPP limits of pressure reactivity is warranted.

Chapter 8

Conclusions and future directions

8.1 Thesis findings in context

Traumatic brain injury has been termed a silent epidemic. With the spread of motorised transport, its prevalence is growing and it has the unfortunate predilection for targeting young adults resulting in devastating health, economic and societal effects. Curbing this epidemic will likely involve cogent public health strategy, but also progress in the management of acutely injured patients. The management of severe TBI requires detailed knowledge of complex intracranial and systemic physiology. Intracranial monitoring offers the possibility for early detection and therefore amelioration of physiological insults.

While intracranial monitoring after severe TBI has been commonplace since the 1950's, whether or not it improves outcome is far from clear. Comparison of centres before and after the implementation of an organised intracranial pressure monitoring protocol generally report improved outcomes, and cross-sectional studies looking at centres with and without intracranial pressure monitoring also show an advantage for ICP monitoring. However, such comparisons can also be explained by confounding factors; an organised ICP monitoring protocol is typically associated with closer monitoring of the patient in general.

Against this backdrop, the BEST TRIP trial compared an ICP monitoring based protocol with an imaging based protocol (aimed at identifying signs of raised ICP) and found no benefit of monitoring ICP in terms of patient outcome. While an impressive study that rightly raises questions about how we manage and monitor TBI patients, the study cannot be used as evidence to not monitor ICP. In a more optimistic study, the RESCUEicp trial demonstrated a mortality benefit of decompressive craniectomy for raised ICP. However this was balanced with the fact that those given a decompressive craniectomy suffered more severe disability. Both these trials highlight the need for a critical look at how we interpret and react to monitored data from our patients.

8.2　Summary of results

In this thesis, I examined cerebral insults due raised intracranial pressure, decreased CPP and impaired vascular pressure reactivity.

In chapter 2, the importance of ICP, CPP and autoregulation in the regulation the cerebral circulation was elucidated along with a summary of the evidence to date supporting autoregulation monitoring in critical illnesses. In chapter 4, ICP, CPP, and PRx insults were demonstrated to be common, prognostically important, and amenable to long term changes in management policies. Further, it was shown that these insults often occur independently, but coexisting insults portend worse prognosis.

In chapter 5, I examined possible clinical antecedents of raised ICP after paediatric traumatic brain injury and found that subarachnoid haemorrhage on the initial CT scan was associated with the subsequent development of elevated ICP on the ICU. In an adult TBI population, elevated glucose during the intensive care stay was associated with worse pressure reactivity but was not related to higher ICP.

The consequences of intracranial hypertension were examined in chapter 6. In a New Zealand rabbit CSF infusion model of raised ICP, I demonstrated cortical perfusion vulnerability and the complementary cerebroprotection provided by the Cushing vasopressor response and reductions in vasomotor tone. Conducting a similar analysis in the rare occurrence of severe refractory intracranial hypertension after TBI (chapter 6), raised ICP was found to disturb cerebral pressure reactivity and can cause ICP pulse amplitude to decrease. Early impairment of pressure reactivity was related to the subsequent development of raised ICP.

In chapter 7, novel applications of intracranial monitoring were proposed including a method to estimate in real-time, the CPP limits of reactivity. The amount of time spent below the individualised CPP lower limit of reactivity was related to worse outcomes, even after adjusting for known predictors such as age, GCS and ICP. Using individualised limits of reactivity may allow for more nuanced treatment in the ICU for TBI but also other neurocritical illnesses. Finally, I explored a recently developed secondary insults visualisation technique, validating it in a large TBI dataset and integrating it with information about the individualised limits of reactivity to show that ICP insults are more harmful if CPP is below the lower limit of reactivity.

8.2.1　Limitations of current work

Common to all the clinical research in this thesis are several limitations that must be considered before generalising the results. The clinical monitoring database allows for associations between intracranial monitoring data and patient outcome, however, this should not be conflated as evidence that improving the intracranial monitoring variable will have any influence on outcome. This would need to be determined with an interventional clinical trial.

Data in each of the chapters are to a large part overlapping, derived from subsets of one database (section 4.2) according to the specific research question. This needs to be appreciated if any subsequent meta-analyses are performed from these data. In addition, the database did not routinely collect clinical events. This is particularly important for future development as the physiological meaning associated with a particular value of ICP or CPP will depend heavily on the intensity of treatment to 'achieve' that value. Finally, further important monitored variables that could have significant influence on intracranial monitoring variables have not been considered here. In particular, arterial CO_2 levels, ventilator settings, blood haematology or biochemistry are important variables to consider in the interpretation of monitoring data, the development of prognostic models and in some cases the development of novel monitoring indices.

The retrospective nature of all reported studies in this thesis also needs to be considered, as this raises the possibility of inclusion bias. The patients included into the research database should in the future be compared with the underlying population (in this case, all severe traumatic brain injury patients entering the neurocritical care unit) to determine whether the included patients in the research database are representative. The patients included in this thesis received specific therapies according to local protocols that aimed to lower ICP and support CPP. Therefore, values lying outside of the local protocol target ranges may represent cases of treatment failure. As alluded to above, a detailed assessment of therapeutic intensity would enhance the interpretation of the data. This is particularly true for the case of decompressive craniectomy; an intervention that can have a significant effect on CPP, ICP and PRx, and possibly, their relationship with outcome. Furthermore, the validity of PRx as an indicator of autoregulation in cases of decompressive craniectomy has not been investigated.

For progress in the field of clinical intracranial monitoring, large multi-centre monitoring databases with informative clinical descriptions and event annotations must be developed. This should ideally be available open access in anonymised form to stimulate novel and reproducible research.

8.3 Future directions

8.3.1 Monitoring based treatment protocols

With increasing knowledge of intracranial physiology has come divergent theories about how best to prevent secondary brain injury. The "Lund concept" espouses the need to avoid potential cerebral damage caused by vasopressors and relies more heavily on volume resuscitation. In such situations, higher values of ICP and lower values of CPP may be tolerated. Some studies albeit with small sample sizes show impressive mortality results using the Lund concept, although its use seems to be confined to Scandinavia and no randomised controlled trials exist. The opposing "CPP-oriented therapy", hinges on using vasopressors to ameliorate the vasodilatory cascade whereby changes in CPP (for example

from decreased MAP) can cause a vicious cycle of cerebral vasodilation and increased ICP. Consistent with this, chapter 4 showed that in time-epochs after the introduction of CPP-oriented therapy, the number of ICP plateau waves decreased.

However, a sound physiological rationale does not guarantee clinical efficacy for a treatment strategy. Although longitudinal studies suggested improved outcomes with the introduction of CPP-oriented therapy, a randomised controlled trial demonstrated that although increased CPP lead to less episodes of cerebral ischaemia, mortality was not improved and rates of acute respiratory distress syndrome were 5 times higher (probably related to vasopressor use).

8.3.2   CPPopt

Thus, indiscriminate CPP augmentation may not be appropriate for every patient and it is probable that permissive low CPP may also not be universally appropriate. Using a third, brain specific physiological marker may allow for an individualised titration of CPP. Emerging cerebral physiological markers such as $P_{BT}O_2$ and pressure reactivity raise the possibility that individually targeted CPP optimisation may superior to both the Lund concept and CPP-oriented therapy. Both autoregulation and $P_{BT}O_2$ targeting are undergoing clinical evaluation (registered clinical trial for CPPopt: NCT02982122 (www.cppopt.org), and for $P_{BT}O_2$ ('Boost 2'): NCT00974259).

It may seem surprising that despite 15 years passing since the first publication outlining a possible CPP optimal therapy after TBI[80], a clinical effectiveness trial has yet to be performed. This seeming lack of progress highlights the difficulties associated with personalised treatment paradigms. Incremental adjustments have however been made: real-time estimates of CPPopt[81], understanding why the method sometimes fails to give values[285], documenting clinicians attitude and interpretation of CPPopt data[286], increasing the availability of optimal CPP estimation to close to 100%[270,273], visualisation of a CPP— autoregulation landscape[275] and most recently, the identification of a safe range of CPP (section 7.1).

8.3.3   Multimodal integration

Although this thesis has focused on ICP, $P_{BT}O_2$ and ABP signals, it should be noted that these represent just a fraction of the information that actually informs clinicians treatment of a patient. Signals pertaining to the patients cardiovascular, biochemical, haematological or respiratory state should ideally be considered with respect to their influence on intracranial monitoring. However, assuming that more information will lead to improved patient outcomes may not be justified. The challenge lies in extracting the most useful features to generate a parsimonious overview that not only describes the patients physiological condition but also informs a personalised therapeutic strategy.

Conclusion

This thesis outlines the prevalence, clinical associations and physiological consequences of secondary insults detected with intracranial monitoring after TBI. Novel analytical techniques are presented that may in the future facilitate clinical integration of intracranial monitoring and clinical decision making.

Appendix A

Additional tables and figures

Table A.1: Physiologic summary of cohort; secondary insults co-occurrence after TBI (n=824; chapter 4.1)

Variable impaired	Hours	% of data
CPP	3334	2.89
ICP	25532	22.11
PRx	26342	22.82
PRx & ICP	6626	5.74
CPP & ICP	1895	1.64
CPP & PRx	1748	1.51
CPP & ICP & PRx	1172	1.02
None of ICP, CPP or PRx	69348	60.06

ICP intracranial pressure; *CPP* cerebral perfusion pressure; *PRx* pressure reactivity index.
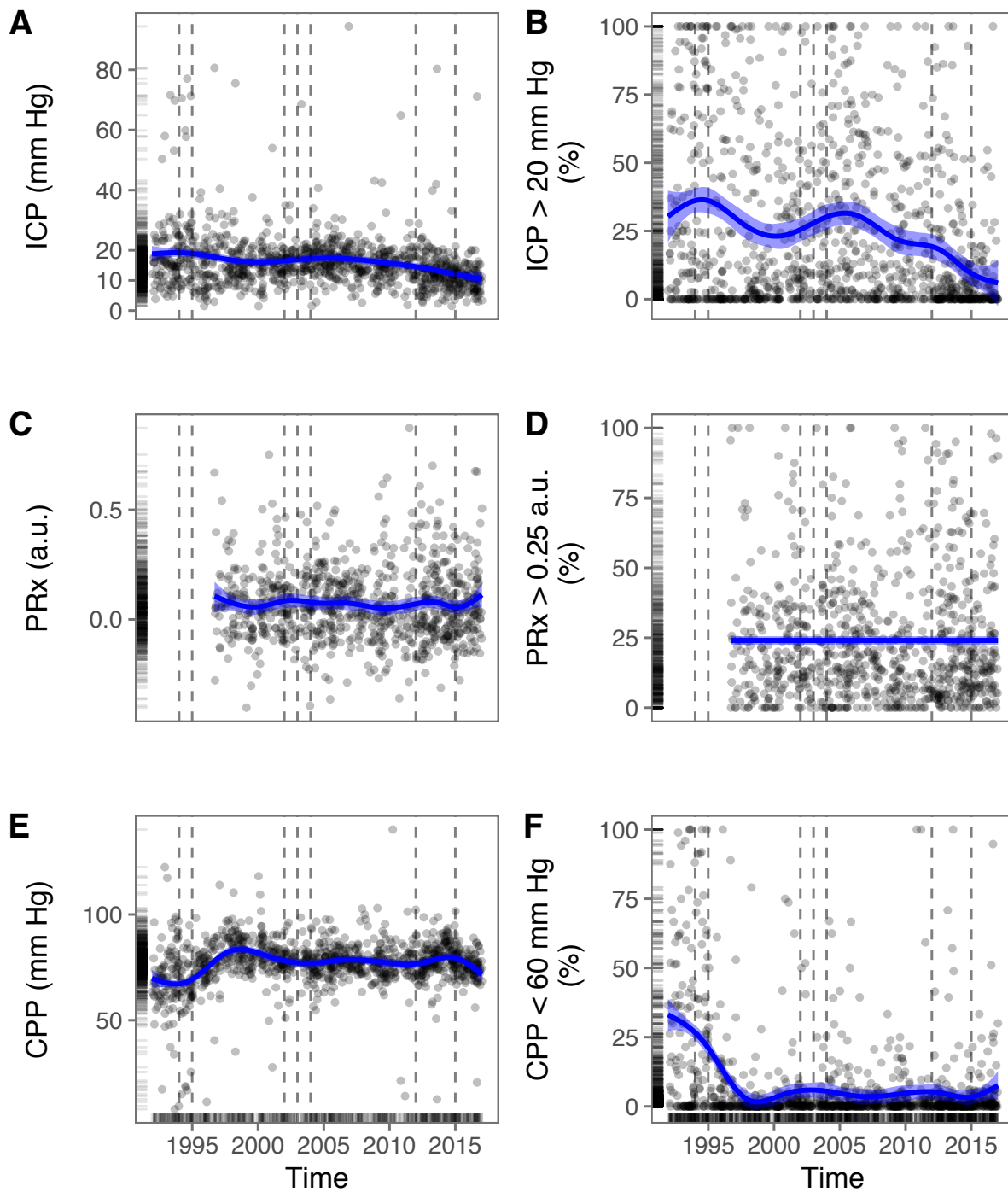
Figure A.1: **Changes in TBI neuromonitoring variables over 25 years- ICP (top), PRx (middle) and CPP (bottom) showing individual data points and trend (n=1110; from section 4.2).** ICP decreases from just below 20 mm Hg to ~12 mm Hg while CPP increases shortly after 1995 from below 70 to greater than 80 mm Hg around 2000. PRx remains unchanged throughout the 20 years it has been monitored. Key changes in management are indicated by the dotted lines and refer to (in chronological order: Change from ward to NCCU based care (1994); introduction of brain oxygen and metabolism monitoring, relaxation of CO_2 and CPP targets (2002-2004), designation of major trauma unit (2012); and switch from ABP transducer zero at heart to brain level (2015). *ICP- intracranial pressure; PRx- pressure reactivity index; CPP- cerebral perfusion pressure.*
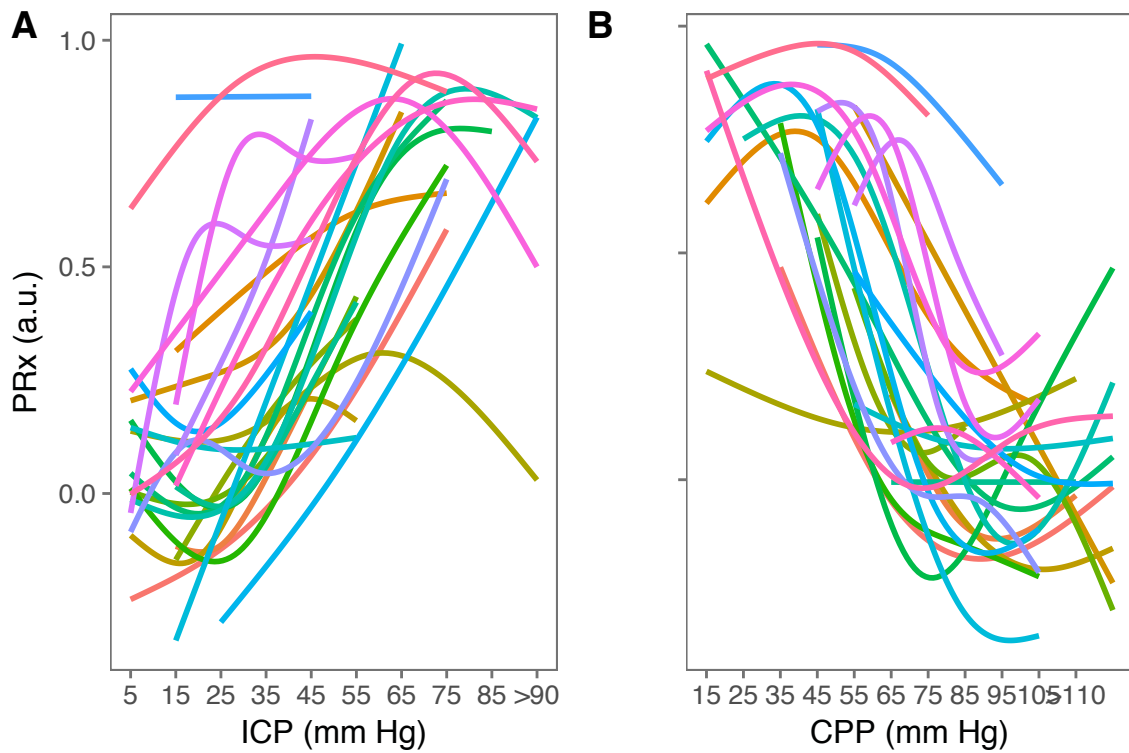
Figure A.2: **Individual PRx responses to refractory intracranial hypertension expressed relative to changes in ICP (left) and CPP (right) (n=24; from section 6.2.1).** Pressure reactivity increased with increasing ICP and PRx plotted against CPP revealed a partial 'U-shaped' curve as previously described. PRx is well maintained until CPP drops below 70 mm Hg, below which PRx deteriorates. *PRx- pressure reactivity; ICP- intracranial pressure; CPP cerebral perfusion pressure.*
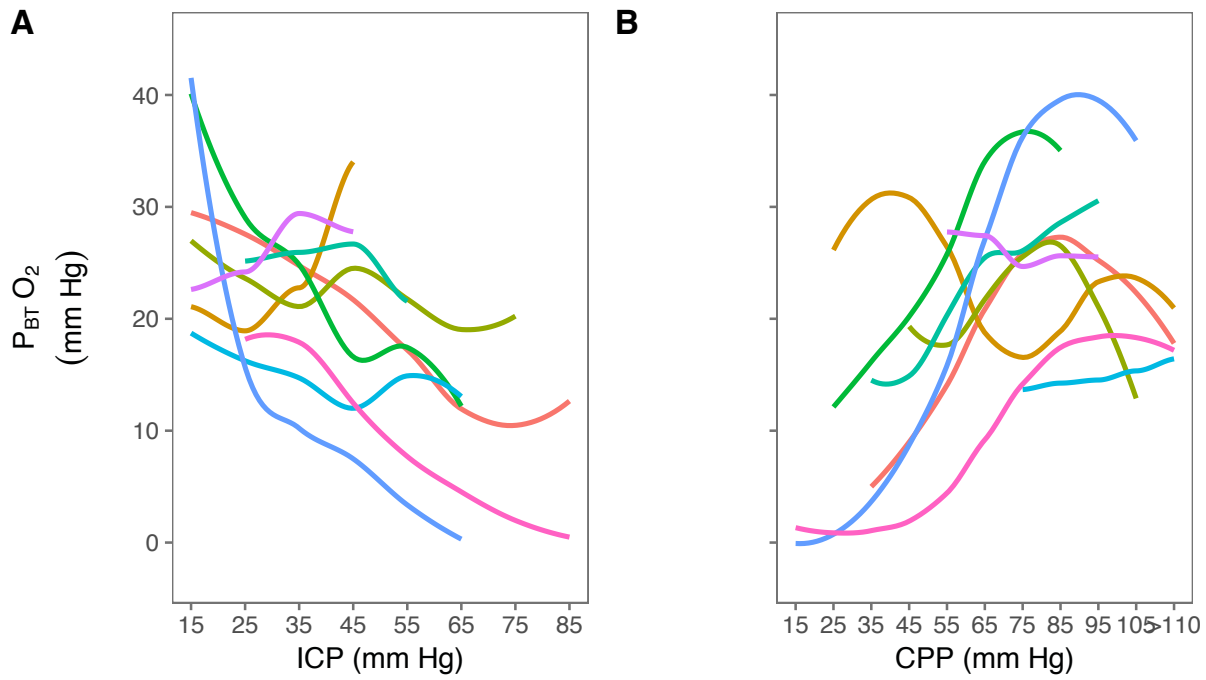
Figure A.3: **Individual $P_{BT}O_2$ response to refractory intracranial hypertension expressed relative to changes in ICP (left) and CPP (right) (n=9; from section 6.2.1)** When expressed against ICP, $P_{BT}O_2$ demonstrates a steady decrease. When expressed in relation to changes in CPP, the relationship resembles the autoregulation curve; with moderate levels of CPP (70 to >90 mm Hg), oxygenation is well maintained, but lower than 70 mm Hg, oxygenation decreases (by approximately 0.5 mm Hg per 1 mm Hg decrease in CPP). *$P_{BT}O_2$- brain tissue oxygenation; ICP- intracranial pressure; CPP- cerebral perfusion pressure.*

Table A.2: ROC AUC for flexible and fixed CPP limits in predicting mortality and unfavourable outcome (from section 7.1)

Variable	AUC Mortality	AUC Unfavourable
%CPP < LLR	0.73 (0.68-0.78)	0.6 (0.56-0.64)
%ΔCPPopt < -10 (mean (sd))	0.66 (0.61-0.71)	0.55 (0.51-0.6)
%CPP < 60	0.64 (0.58-0.69)	0.56 (0.52-0.6)
%CPP > ULR	0.5 (0.45-0.55)	0.55 (0.51-0.59)
%ΔCPPopt > 10 (mean (sd))	0.42 (0.36-0.47)	0.48 (0.44-0.53)
% CPP > 70	0.36 (0.31-0.41)	0.52 (0.47-0.56)

CPP cerebral perfusion pressure; *ΔCPPopt* cerebral perfusion pressure minus cerebral perfusion pressure optimal; *LLR* lower limit of reactivity; *ULR* upper limit of reactivity; *AUC* area under the (receiver operating characteristic) curve.

Table A.3: Multivariable outcome analysis for unfavourable outcome; individualised CPP thresholds after TBI (from section 7.1)

Statistic	% CPP<LLR	p	%ΔCPPopt <-10	p	%CPP <60	p
% CPP < LLR (OR)	1.04 (1.02-1.05)	<0.001				
% ΔCPPopt < -10 (OR)			1.02 (1-1.03)	0.020		
% CPP<60 (OR)					1.03 (1.01-1.05)	0.010
ICP (mm Hg) (OR)	1.05 (1.02-1.09)	<0.001	1.06 (1.03-1.09)	<0.001	1.05 (1.02-1.09)	0.000
Intercept (OR)	0.4 (0.19-0.82)	0.010	0.37 (0.18-0.75)	0.010	0.42 (0.21-0.85)	0.020
Age (OR)	1.04 (1.03-1.05)	<0.001	1.04 (1.03-1.05)	<0.001	1.04 (1.03-1.05)	<0.001
GCS (OR)	0.82 (0.78-0.86)	<0.001	0.82 (0.78-0.86)	<0.001	0.82 (0.78-0.86)	<0.001
AIC	885.75		901.14		904.76	
Log-Likelihood ratio	-437.87		-445.57		-447.38	
AUC	0.75		0.74		0.74	

CPP cerebral perfusion pressure; *OR* odds ratio; *ICP* intracranial pressure; Δ*CPPopt* cerebral perfusion pressure minus cerebral perfusion pressure optimal; *LLR* lower limit of reactivity; *GCS* Glasgow coma scale; *AIC* Akaike information criteria; *AUC* area under the (receiver operating characteristic) curve.

Appendix B

Publications from thesis

1. Donnelly, J., & Czosnyka, M. (2014). The thermodynamic brain. Critical Care, 18(6), 693.

2. Donnelly, J., Aries, M. J., & Czosnyka, M. (2015). Further understanding of cerebral autoregulation at the bedside: Possible implications for future therapy. Expert Review of Neurotherapeutics, 15(2), 169–185.

3. Donnelly, J., Czosnyka, M., Adams, H., Robba, C., Steiner, L. A., Cardim, D., ... Smielewski, P. (2017). Individualizing thresholds of cerebral perfusion pressure using estimated limits of autoregulation. Critical Care Medicine, 45(9), 1464–1471.

4. Donnelly, J., Czosnyka, M., Harland, S., Varsos, G. V., Cardim, D., Robba, C., ... Smielewski, P. (2017). Cerebral haemodynamics during experimental intracranial hypertension. Journal of Cerebral Blood Flow & Metabolism, 37(2), 694–705.

5. Donnelly, J., Czosnyka, M., Sudhan, N., Varsos, G. V., Nasr, N., Jalloh, I., ... Smielewski, P. (2015). Increased blood glucose is related to disturbed cerebrovascular pressure reactivity after traumatic brain injury. Neurocritical Care, 22(1), 20–25.

6. Donnelly, J., Budohoski, K. P., Smielewski, P., & Czosnyka, M. (2016). Regulation of the cerebral circulation: Bedside assessment and clinical implications. Critical Care, 20(1), 129.

7. Donnelly, J.*, Young A.*, Smielewski, P.,Czosnyka, M. 2017. Early imaging indicators of increased ICP after paediatric traumatic brain injury. Acta Neurochirurgica. Accepted article.

Appendix C

Co-authored publications during PhD

1. Adams, H., Donnelly, J., Czosnyka, M., Kolias, A. G., Helmy, A., Menon, D. K., ... Hutchinson, P. J. (2017). Temporal profile of intracranial pressure and cerebrovascular reactivity in severe traumatic brain injury and association with fatal outcome: An observational study. PLoS Medicine, 14(7), e1002353.

2. Andresen, M., Donnelly, J., Aries, M., Juhler, M., Menon, D., Hutchinson, P., & Smielewski, P. (2017). Further controversies about brain tissue oxygenation pressure-reactivity after traumatic brain injury. Neurocritical Care, 1–7.

3. Aries, M. J., Wesselink, R., Elting, J. W. J., Donnelly, J., Czosnyka, M., Ercole, A., ... Smielewski, P. (2016). Enhanced visualization of optimal cerebral perfusion pressure over time to support clinical decision making. Critical Care Medicine, 44(10), e996–e999.

4. Aries, M., Regtien, J., Czosnyka, M., Donnelly, J., & Smielewski, P. (2015). Neuromonitoring of patients with severe traumatic brain injury at the bedside. Critical Care, 19(1), P451.

5. Bain, A. R., Ainslie, P. N., Bammert, T. D., Hijmans, J. G., Sekhom, M., Hoiland, R. L., ... DeSouza, C. A. (2017). Passive heat stress reduces circulating endothelial and platelet microparticles. Experimental Physiology.

6. Burgess, K. R., Lucas, S. J., Shepherd, K., Dawson, A., Swart, M., Thomas, K. N., ... others. (2014). Influence of cerebral blood flow on central sleep apnea at high altitude. Sleep, 37(10), 1679–1687.

7. Cabella, B., Donnelly, J., Cardim, D., Liu, X., Cabeleira, M., Smielewski, P., ... Czosnyka, M. (2017). An association between icp-derived data and outcome in tbi patients: The role of sample size. Neurocritical Care, 27(1), 103–107.

8. Calviello, L. A., Riva, N. de, Donnelly, J., Czosnyka, M., Smielewski, P., Menon, D. K., & Zeiler, F. A. (2017). Relationship between brain pulsatility and cerebral perfusion pressure: Replicated validation using different drivers of cpp change. Neurocritical Care, 1–9.

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