Neurointensive Care of Children with Severe Traumatic Brain Injury

Studies of barbiturate coma treatment, intracranial compliance, pressure autoregulation and optimal cerebral perfusion pressure

FARTEIN VELLE
Traumatic brain injury (TBI) is among the most common causes of death and acquired disability during childhood. Management guidelines for pediatric patients are usually extrapolated from adults. Specific pediatric studies are warranted to improve the TBI management in children.

A modern neurointensive care (NIC) unit, with standardized care and advanced computerized multimodality monitoring and data collection systems, offers an unique platform for explorative research.

The general aims of this thesis were to increase the knowledge on barbiturate coma treatment (BCT) for refractory intracranial hypertension (RICH) and on cerebral pressure autoregulation (CPA) of cerebral blood flow, in pediatric TBI.

**Paper I** - Twenty-one children were included with severe TBI who developed RICH despite first-tier therapy. BCT proved to be effective in lowering ICP without causing severe side effects, when used in a modern NIC setting. BCT resulted in relatively good long-term outcome.

**Paper II** - High resolution (100 Hz) monitoring data were analyzed in 17 TBI children with RICH. BCT reduced ICP significantly and improved intracranial compensatory reserve (RAP-index) while cerebral perfusion pressure (CPP) was maintained. **Paper III** - High resolution (100 Hz) monitoring data from 57 children with TBI were analyzed for assessment of CPA status according to the pressure reactivity index (PRx), calculation of optimal CPP (CPPopt) and assessment of deviations from CPPopt (ΔCPPopt). Impaired CPA was related to poor outcome and actual CPP below the CPPopt level contributed significantly to unfavorable outcome in children < 15 years. CPPopt appeared to be higher after a few days when CPA was most impaired. **Paper IV** - The metabolic state of the brain was assessed in 21 children with cerebral microdialysis (CMD) and related to actual CPP levels, PRx, CPPopt and ΔCPPopt. Increased levels of CMD lactate and the lactate/pyruvate ratio (LPR) (markers of ischemia) were related to disturbed CPA (higher PRx), actual CPP levels ≥70 mmHg and when actual CPP was above CPPopt, respectively.

The findings in this thesis indicate that BCT may be an effective option for treatment of RICH in pediatric TBI and that individualized CPA guided CPP management may be beneficial, at least in younger TBI children.

**Keywords:** Traumatic brain injury, Children, Refractory intracranial hypertension, Barbiturate coma, Intracranial compensatory reserve, autoregulation, cerebral microdialysis.
Till Réka, Otilia, Isolde och Endre
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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<td>ABP</td>
<td>Arterial blood pressure</td>
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<td>BCT</td>
<td>Barbiturate coma treatment</td>
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<td>CBF</td>
<td>Cerebral blood flow</td>
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<tr>
<td>CMD</td>
<td>Cerebral microdialysis</td>
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<td>CMRO₂</td>
<td>Cerebral metabolic rate of oxygen</td>
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<td>CPA</td>
<td>Cerebral pressure autoregulation</td>
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<tr>
<td>CPP</td>
<td>Cerebral perfusion pressure (MAP – ICP)</td>
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<td>CPPopt</td>
<td>Optimal cerebral perfusion pressure</td>
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<tr>
<td>ΔCPPopt</td>
<td>Deviation from CPPopt</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>CVD</td>
<td>Cerebral vascular diameter</td>
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<tr>
<td>CVP</td>
<td>Central venous pressure</td>
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<td>DC</td>
<td>Decompressive craniectomy</td>
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<td>EDH</td>
<td>Epidural hematoma</td>
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<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<td>EVD</td>
<td>External ventricular drain</td>
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<td>GCS</td>
<td>Glasgow coma scale</td>
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<td>GCSm</td>
<td>Glasgow coma scale motor score</td>
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<tr>
<td>GOS</td>
<td>Glasgow outcome scale</td>
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<tr>
<td>GMT</td>
<td>Good monitoring time</td>
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<tr>
<td>%GMT</td>
<td>Percentage of good monitoring time</td>
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<tr>
<td>ICH</td>
<td>Intracerebral hematoma</td>
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<td>ICP</td>
<td>Intracranial pressure</td>
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<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>KOSCHI</td>
<td>King’s outcome scale for childhood head injury</td>
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<td>LPR</td>
<td>Lactate/Pyruvate ratio</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
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<tr>
<td>NIC</td>
<td>Neurointensive care</td>
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<td>NICU</td>
<td>Neurointensive care unit</td>
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<td>PRx</td>
<td>Pressure reactivity index (autoregulation)</td>
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<td>RAP index</td>
<td>Cerebrospinal compensatory reserve</td>
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<tr>
<td>RICH</td>
<td>Refractory intracranial hypertension</td>
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<tr>
<td>aSDH</td>
<td>Acute subdural hematoma</td>
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<td>TBI</td>
<td>Traumatic brain injury</td>
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Introduction

Traumatic brain injury (TBI) in childhood is a common cause of death and acquired disability in the developed world and even more so in less-developed parts of the world. According to recent publications, the estimated annual median incidence of childhood TBI in North America, Europe, Australia, and New Zealand is: 691 per 100,000 people treated in emergency departments, 74 per 100,000 hospitalized, and 9 per 100,000 results in death. According to the Swedish national board of health and welfare, the total overall annual death rate in Sweden in the age group 1–14 years is 8 per 100,000. Neurotrauma deaths account for 1/100,000 per year in the same patient group, but was twice as high a decade earlier (http://nowbase.org). Of Sweden’s 1.9 million children (0–17 years old), approximately 18,300 children were hospitalized due to trauma in 2014 and 3600 of these admissions were due to TBI. During 2014, 160 per 100,000 children in Sweden aged 0–14 years were diagnosed with intracranial injury and 5.4 per 100,000 required cranial surgery that was related to the trauma.

Moderate and severe TBI require neurointensive care (NIC) to prevent secondary insults (e.g. raised intracranial pressure – ICP, hypoxia and hypotension) to the injured brain and to optimize the cerebral environment in order to achieve the best possible long-term outcome. Despite first-tier therapy of raised ICP - treated by means of surgical evacuation of mass lesions and cerebrospinal fluid (CSF) drainage, some patients still develop refractory intracranial hypertension (RICH). In many NIC units, RICH is treated with barbiturate coma. Barbiturate coma treatment (BCT) in adults is a well established practice, but many neurosurgical centers have a more restrictive attitude toward this treatment in children. The reasons for this include unclear outcome results and risk of adverse events related to the toxic effects of barbiturates.

In order to improve clinical outcome, it is important to gain more knowledge on how secondary insults affect the primary brain injury during NIC. Advanced computerized multimodality monitoring and data collection systems make studies of the injured brain’s vulnerability to secondary insults and the underlying mechanisms for secondary brain injury possible. New management concepts may also be developed. Studies on NIC high frequency
monitoring data have over the last decade improved our understanding regarding ICP dynamics, cerebral perfusion pressure (CPP) management, intracranial compliance, cerebrovascular pressure reactivity and optimal cerebral perfusion pressure (CPPopt). This improved knowledge is, however, mainly based on studies of the adult population. Treatment considerations in children differ in several aspects from adults due to the anatomical and physiological development in children\textsuperscript{15,16}. These differences probably affect CPP levels, cerebrovascular pressure autoregulation (CPA) of cerebral blood flow (CBF) and intracranial compliance\textsuperscript{17-20} that in turn influence secondary insult levels.

Altogether, further studies are needed in children regarding various aspects of BCT (e.g., clinical outcome, treatment-related complications, and effects on ICP, mean arterial pressure (MAP), CPP and intracranial compliance, respectively). It is also necessary to obtain more knowledge overall about CPA and optimal CPP, specifically in children.
Background

Anatomical and physiological characteristics of children and adolescents

In children there are developmental differences in anatomical and physiological characteristics compared to adults that need to be taken into account in the management of TBI\textsuperscript{15}. This includes both the central nervous system and the body in general. First, there are different inter-body weight proportions that result in other kinetic forces for younger children when exposed to trauma. Younger children have a relatively larger head, thinner and more pliable cranium and cranio-cervical junction, lesser inter-vertebral strength and more immature spinal ligaments and muscles. Moreover, the airway is easily compromised, the chest is poorly protected and the abdominal organs are large. A systemic physiological difference to consider in children is their relatively higher blood-volume per kilo, but lesser total blood volume compared to adults.

Regarding intracranial dynamics, open fontanels and cranial sutures increase the ability to compensate for added intracranial volume, while a relatively larger brain and less cerebrospinal fluid decrease the compensatory volume reserve (compliance). In children the normal CPP is lower because normal blood pressure is lower and therefore critical CPP thresholds are also different. Normal CPP also changes with increasing age. The intracranial pathologies may also differ, e.g., in children diffuse traumatic brain injuries are more common\textsuperscript{21,22}.

Mechanisms of Barbiturates

Barbiturates are lipophilic, fast-acting drugs that easily cross the blood brain barrier. Barbiturates reduces oxygen metabolism (CMRO\textsubscript{2}) whereby a coupled metabolic regulation decrease CBF and cerebral blood volume (CBV) which leads to decrease of ICP\textsuperscript{23}. As a result, CPP increases and oxygen transport improves. The decrease of CMRO\textsubscript{2} also reduces the oxygen demand. Altogether, the metabolic state may improve and turn from anaerobic to aerobic metabolism, i.e., ischemia is reversed.
Barbiturates are thought to protect the injured brain by several direct mechanisms. On a cellular level, barbiturates bind to the GABA-A receptor and activate chloride channels. The increased chloride ion flux results in GABA-induced post-synaptic inhibition. Activation of GABA-A receptor is one explanation of the protective mechanisms on the injured brain. Another positive effect is that barbiturates decrease the release of the excitatory amino acids glutamate and aspartate and thereby decrease neurocellular excitotoxicity. The non-selective binding to other ligand-gated ion channels explains side-effects such as cardiovascular depression resulting in hypotension.

Cerebral pressure autoregulation

In healthy individuals, CPA keeps CBF constant within a certain range of CPP levels to protect the brain from hypoperfusion and hyperemia when systemic blood pressure changes within normal ranges. As a result of TBI this autoregulatory mechanism may be disturbed, which increases vulnerability of the brain to potentially harmful blood pressure events of hypoperfusion causing ischemia or hyperemia causing edema and thereby increasing intracranial pressure (ICP). A surrogate marker of CPA is the pressure reactivity index (PRx) which is calculated as a moving correlation coefficient between the MAP and ICP based on their spontaneous slow fluctuations. A negative PRx indicates intact pressure reactivity of active cerebral vasculature, i.e., a decrease in MAP results in cerebral vessel dilation which increases ICP (pressure active) (Fig. 1A). A positive PRx indicates impaired cerebral vessel reactivity due to passive cerebral vasculature, i.e., a decrease in MAP results in passive cerebral vasoconstriction that decreases cerebral blood volume and thereby also ICP (pressure passive) (Fig. 1B).
Figure 1. Illustration of intact (A) and disturbed (B) pressure autoregulatory mechanism. A - Changes in MAP cause compensatory changes in cerebral vessel diameter and thereby vessel resistance to keep CBF stable. The subsequent changes in cerebral blood volume cause reciprocal ICP changes. The correlation index between MAP and ICP is negative (PRx<0). B - Changes in MAP do not cause a compensatory cerebral vessel response. The correlation index between MAP and ICP is positive (PRx>0). MAP - mean arterial pressure, CBF - cerebral blood flow, ICP - intracranial pressure, ABP - arterial blood pressure, CVD - cerebral vascular diameter.

The CPP associated with the most negative PRx may be regarded as the optimal CPP level (CPPopt), i.e., the CPP level where CPA works best\(^{39-41}\) (Fig. 2). The best threshold target for CPP is not completely elucidated in adults and there exists even less data on optimal thresholds for children\(^{42}\). Instead of using fixed targets for CPP, PRx directed targets for CPP could be beneficial in NIC\(^{39-41,43}\). A recent multicenter randomized controlled trial (COGiTATE)\(^{44}\) found that such treatment was feasible and safe in adults. There are plans for prospective studies powered for implications of CPPopt guided treatment on clinical outcome. So far studies of CPA have been mainly focused on adults, but there is need to carry out similar studies on children\(^{17,45-49}\).
Cerebrospinal compensatory reserve

Intracranial compliance is the ability to compensate for increases in added intracranial volume, i.e., cerebrospinal compensatory reserve. This can be expressed by the RAP index, which is based on the correlation (Pearson’s R) between the amplitude of the ICP pulse wave and mean ICP (ICP_Amp/ICP)\(^50\). Mean ICP pulse amplitude and mean ICP is calculated for 10-second sequences and the correlation is calculated over a 5-minute window using those values. The moving 5-minute window is advanced in 12-second increments, so that five correlation values are produced per minute\(^36,37,50,51\). A RAP index close to 0 indicates lack of synchronization between these two parameters; a change in volume produces no or very little change of pressure amplitude, which denotes a good pressure-volume compensatory reserve (usually at low ICP levels). On the other hand, when RAP rises to +1 (positive linear relationship), the amplitude varies directly with ICP which denotes a low compensatory reserve. With further rise in volume, ICP rises rapidly and eventually the amplitudes decrease, and RAP values becomes negative, towards -1 (negative linear relationship). This happens when the cerebral autoregulation capacity is exhausted, cerebral arterioles passively collapse instead of dilating as a response to decreased perfusion (Fig. 3).
Cerebral microdialysis

Cerebral microdialysis (CMD) is a minimally invasive technique to monitor chemical changes in the extracellular fluid that was introduced in NIC 1992\textsuperscript{52}. By using CMD the cerebral metabolic state of the brain can be assessed\textsuperscript{53,54}. Lactate and the lactate/pyruvate ratio (LPR) are markers of ischemia, where LPR is the main index of cellular redox state and the balance between oxidative and anaerobic metabolism\textsuperscript{55}. In our department the MD catheter is inserted in non-lesioned brain in order to measure effects of global events such as high ICP.

Only a few studies have been published on CMD in children and adolescents with severe TBI\textsuperscript{56-58} and there are no CMD studies with focus on CPA. Tolias et al.\textsuperscript{58} found significant fluctuations of CMD glutamate (excitatory amino acid transmitter), but no correlation to ICP/CPP changes in children with TBI. Thango et al.\textsuperscript{57} studied CMD glycerol (marker of cell damage and hypoxia) in children with severe TBI. They found a strong relationship with lesion progression on head CT. They also found an association between CMD glycerol and ICP and brain oxygenation (PbtO\textsubscript{2}), respectively, but no association with clinical outcome.
A more direct indicator of the potential advantage of targeting CPPopt than clinical outcome would be to study the metabolic state of the brain in relation to CPA status and deviations from CPPopt.
Aims of the investigations

General aim
The general aims of this thesis on pediatric traumatic brain injury were to increase the knowledge about barbiturate coma treatment and the knowledge about cerebral pressure autoregulation, in order to ultimately refine neurointensive care and improve clinical outcome in this particular group of patients.

Specific aims

Paper I
To evaluate the long-term clinical outcome and occurrence of treatment-related complications when BCT was used as last tier treatment in children with RICH due to severe TBI in a modern NICU setting.

Paper II
To evaluate the effects of BCT on ICP, MAP, CPP and compliance/intracranial compensatory volume reserve (RAP-index) in children with RICH due to severe TBI at time intervals before, during and after onset of BCT.

Paper III
To investigate cerebral pressure autoregulation (PRx), CPP, CPPopt and deviations from CPPopt (ΔCPPopt) during neurointensive care of children with moderate and severe TBI in general, and in more detail regarding age relations, temporal changes and the influence on outcome.

Paper IV
To relate metabolic markers of ischemia (lactate and lactate/pyruvate ratio - LPR) monitored by cerebral microdialysis (CMD) to actual CPP levels, PRx, CPPopt and ΔCPPopt in children with severe TBI in order to evaluate the potential of individualized CPPopt guided management in those age groups.
Materials and Methods

Patient selection, data collection and calculation of different physiological measures

The Department of Neurosurgery, Uppsala University Hospital, serves 7 counties in the middle part of Sweden with a total catchment area of about 2 million people. Primary cases admitted for neurointensive care (NIC) come from Uppsala County and secondary cases from local hospitals in the other counties, located within a distance of about 300 km.

Children (≤ 17 years) studied in this thesis suffered from moderate to severe TBI (GCSm ≤5), and were intubated and mechanically ventilated and had ICP monitoring. Monitoring data were obtained from the Odin monitoring system at the NICU, which is routinely used for visualization of monitoring data bedside and computerized collection of monitoring data (minute and high resolution) for quality assurance and research.

The RAP index was calculated in Odin. Mean ICP pulse amplitude and mean ICP was calculated for 10-second sequences and the correlation (Pearson’s R) was calculated over a 5-minute window using those values. The moving 5-minute window was advanced in 12-second increments, so that five correlation values were produced per minute (Fig. 3).

PRx was calculated as a moving 5-min correlation of 10 sec averages of high resolution ICP and MAP in Odin (Fig. 1). CPPopt was calculated as the CPP with the lowest PRx during the previous 4 hours (Fig. 2). Deviations from CPPopt were denoted ΔCPPopt and calculated as the difference between actual CPP and CPPopt. ΔCPPopt was presented as percentage of good monitoring time (%GMT) with ΔCPPopt < -10, ±10 or > 10, respectively.

Intracerebral microdialysis

CMD samples were collected by a catheter that was routinely placed in the right frontal lobe in non-lesioned tissue, through a separate burr-hole close to the intracranial monitoring device. A 71 High Cut-Off microdialysis catheter
was used with a membrane length of 10 mm and a membrane cutoff of 100 kDa (M Dialysis AB, Stockholm, Sweden). The catheters were perfused by custom made sterile artificial cerebrospinal fluid (NaCl 147 mmol/L, KCl 2.7 mmol/L, CaCl₂ 1.2 mmol/L, and MgCl₂ 0.85 mmol/L supplemented with 1.5% human albumin (Perfusion Fluid CNS, M Dialysis AB) using a microinjection pump (106 MD Pump, M Dialysis AB) at a rate of 0.3 µL/min. The CMD samples were collected hourly and analyzed bedside using either the CMA600 or the ISCUSflex Microdialysis Analyzer (M Dialysis AB). Routine calibrations were performed.

NIC Procedures and Patient Management

Uppsala has a dedicated NICU with protocol based management according to a standardized treatment protocol with specific focus on identifying and treating secondary insults\(^4\). The main focus for all levels of the staff is to minimize the occurrence of secondary insults and the development of secondary brain injury. Specific treatment threshold goals are defined in the protocol (Fig.4). All documentation is visualized and recorded in an electronic patient data management system. Specific interfaces have been created for daily rounds and check-lists are filled out documenting the occurrence of secondary insults in the end of the nurse shifts\(^6\).

Neurological state (GCSmotor)\(^6\) (Table 1) is assessed regularly by wake-up tests if the patient has stable ICP. All admitted patients not responding to commands (GCSm ≤ 5) are routinely intubated, and in the acute phase mild hyperventilation (pCO₂ 4–4.5 kPa / 30–34 mm Hg) is applied until ICP monitoring is introduced. The patients are normoventilated as soon as ICP permits. All patients with GCSm ≤ 5 receive an ICP monitor, preferably an external ventricular drain (EVD).

Sedation and analgesia is maintained with infusions of propofol and injections of morphine, respectively. In children, propofol is replaced by midazolam. The patients are kept normovolemic with adequate colloid osmotic pressure. Sodium concentrations are kept around 140 mmol/L. Zero or slightly negative water balance is aimed and central venous pressure (CVP) is maintained at 0–5 mm Hg. Albumin (20%) infusions are used to maintain intravascular colloid osmotic pressure (Albumine 5% in very small children). Cristalloids and albumin, dobutamine and finally noradrenaline are administered if hypotension occurs.

The NIC management in Uppsala is ICP oriented and primarily not CPP oriented. The Basic principles are as follows. The goal is to keep ICP < 20 mm Hg and CPP around 60 mm Hg in adults and as low as 45–50 mm Hg is accepted in children depending on age. During BCT, CPP levels down to 50 mm Hg are
accepted in adults and 40–45 mm Hg in children. In cases of high ICP, active increase of blood pressure above normal levels in order just to obtain an adequate CPP is not prescribed. Spontaneous CPP levels over 60 mm Hg are not actively lowered unless the raised CPP has a detrimental effect on ICP levels. The aim of this strategy is to prevent the development of secondary brain edema in tissue with a disturbed blood-brain barrier and/or cerebral vascular autoregulation. No specific treatments for CMD disturbances were used. Instead, the CMD monitoring was used as an early warning system for emerging treatable secondary insults.

If ICP increases despite this basal therapy, a re-evaluation of the occurrence of secondary insults is conducted and a new CT scan is performed to rule out surgical mass lesions before escalation of ICP therapy to Step 1 therapy. This escalated therapy includes: deeper sedation and more morphine; stress reduction with beta-blockers in the form of metoprolol and centrally acting alpha-adrenergceptor stimulators (clonidine); and intermittent drainage of CSF from an EVD if possible. If there is no radiological sign of an expanding mass lesions, the intermittent drainage of CSF can, after some time (1–2 days), be changed to continuous drainage against a pressure level of 15–20 mm Hg.

If these measures do not alleviate ICP problems, Step 2 therapy is initiated. A new re-evaluation of all parameters is performed and if cerebral CT shows no significant mass lesion or midline shift, BCT is initiated. Osmotherapy is not included in the protocol. Thiopental infusion is used as a monosedative (pentocur®, Abcur AB) in the lowest necessary dose to decrease ICP. Burst suppression on electroencephalography (EEG) is not a primary goal. The strategy of using the lowest possible dose to decrease ICP is intended to minimize the risk of barbiturate-related complications. BCT is initiated with thiopental boluses given as small repeated doses (50-mg doses in adults and between 10 and 50 mg doses in children depending on weight) until ICP normalizes (total 8–10 mg/kg in adults and 3–5 mg/kg in children). Intermittent doses are given to ensure that there is minimal effect on MAP. A continuous infusion of thiopental is started at the same time as the boluses are given (initial dose 5–10 mg/kg/hr), which is adjusted over time depending on ICP levels, suppression periods on EEG, and serum concentrations of thiopental. The EEG monitoring is primarily used to observe and prevent excessive thiopental doses causing long periods of suppression. Furthermore, it is possible to increase the dose in case of persistently high ICP if there is no burst-suppression on EEG. Serum thiopental levels less than 300 μmol/L are the preferred primary serum concentration levels to avoid complications. Patients receive only parenteral nutrition during BCT. Patients are kept on thiopental as short a time as possible depending on clinical status, interpretation of intracranial dynamics (mean ICP, amplitude, and plateau waves), CT brain findings, and severity of complications.
If ICP cannot be controlled in this way or if the side effects are too severe, a decompressive craniectomy (DC) is performed, Step 3 therapy. If the patient has a diffuse mass lesion with significant shift of the mid-line, BCT is considered contra indicated and a DC is performed instead of initiating BCT. A DC may also be performed primarily in association to acute evacuation of hematomas if considered necessary.

Table 1. Glasgow Coma Scale (GCS)\(^6\). Best sum score of motor, verbal and eye response.

<table>
<thead>
<tr>
<th>GCS</th>
<th>Motor response</th>
<th>Verbal response</th>
<th>Eye response</th>
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<tbody>
<tr>
<td>6</td>
<td>Obeys command</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Localizes pain</td>
<td>Oriented</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Withdrawal to pain</td>
<td>Confused</td>
<td>Spontaneously</td>
</tr>
<tr>
<td>3</td>
<td>Abnormal flexion</td>
<td>Inappropriate words</td>
<td>To speech</td>
</tr>
<tr>
<td>2</td>
<td>Abnormal extension</td>
<td>Inappropriate sounds</td>
<td>To pain</td>
</tr>
<tr>
<td>1</td>
<td>No response</td>
<td>No response</td>
<td>No response</td>
</tr>
</tbody>
</table>
**Uppsala Neurointensive care management protocol**

**Pediatric TBI**

GCSm ≤ 5

**Basal management**

- Intubation, mild hyperventilation.
- Sedation: Propofol (Midazolam <15yrs)
- Analgesia: Morphine.
- ICP monitoring (EVD/parenchymatous)
- CMD monitoring (individualized).
- Head elevation 30°.
- Wake-up tests regularly.
- Albumin 20% (5% in smaller children).
- Crystalloids.
- Inotropes if necessary.
- Evacuation of CT mass lesions.

**ICP>20 mmHg**

- Re-evaluation if secondary insults.
- Evacuation of CT mass lesions.
- Intermittent CSF drainage via EVD.
- Increase of sedation/analgesia.
- Clonidine and metoprolol.
- No wake-up tests.

**ICP≤20 mmHg**

- Continue current therapy

**Step 1**

**ICP>20 mmHg**

- Re-evaluation if secondary insults.
- Initiation of BCT, directed by ICP.
- CPP >50/45/40 mmHg depending on age.
- Step 3 if severe BCT side effects.
- Step 3 directly if diffuse mass lesion.

**ICP≤20 mmHg**

- Continue current therapy

**Step 2**

**ICP>20 mmHg**

- Decompressive craniectomy
  - (No midline – bilateral)
  - (Diffuse mass lesion - unilateral).

**ICP≤20 mmHg**

- Continue current therapy

**Step 3**

- Treatment goals
  - ICP<20 mmHg.
  - CPP>60/50/45 mmHg (depending on age)
  - BPsys>100/90/80 mmHg (depending on age)
  - CVP 0-5 mmHg
  - PO2>12 kPa.
  - PCO2 – Normoventilation when ICP permits
  - SaO₂ >96%
  - Electrolytes-normal ranges (K>2.3mmol/L BCT)
  - B-Glucose 5-10 mmol/L
  - Temperature <38 °C
  - Normovolemia to slight neg balance
  - Adequate colloid osmotic pressure
  - Hb > 100 g/L

**Figure 4.** Uppsala Neurointensive care treatment goals and management protocol. TBI = traumatic brain injury; GCSm = Glasgow coma scale motor score; ICP = intracranial pressure; CPP = cerebral perfusion pressure; ABPsystolic = arterial blood pressure systolic; CVP = central venous pressure; HOB = head of bed elevation; EVD = external ventricular drain; CSF = cerebrospinal fluid; CMD = cerebral microdialysis; BCT = barbiturate coma treatment; CT = computed tomography.
Patient follow up and outcome

In Paper I, outcome was evaluated by GOS\textsuperscript{65} (Table 2) and KOSCHI score\textsuperscript{66-68} (Table 3) at 1 year based on information from patient rehabilitation records.

In Paper II and III clinical outcome was evaluated by GOS\textsuperscript{65} (Table 2) at 1 year based on information from patient rehabilitation records and Uppsala Traumatic Brain Injury register\textsuperscript{69}. GOS 1-3 was considered as unfavorable outcome and GOS 4-5 as favorable.

In Paper IV GOS\textsuperscript{65} (Table 2) was evaluated at around 6 months.

\textbf{Table 2.} Glasgow Outcome Scale (GOS)\textsuperscript{65}.

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<tr>
<th>GOS level</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Dead</td>
</tr>
<tr>
<td>2</td>
<td>Vegetative State</td>
</tr>
<tr>
<td>3</td>
<td>Severe Disability</td>
</tr>
<tr>
<td>4</td>
<td>Moderate Disability</td>
</tr>
<tr>
<td>5</td>
<td>Good recovery</td>
</tr>
</tbody>
</table>
Table 3. King’s Outcome Scale for Childhood Head Injury (KOSCHI)\textsuperscript{56-68}.

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1: Death</strong></td>
<td>The child is breathing spontaneously and may have sleep/wake cycles. He may have non-purposeful or reflex movements of limbs or eyes. There is no evidence of ability to communicate verbally or non-verbally or to respond to commands.</td>
</tr>
<tr>
<td><strong>2: Vegetative</strong></td>
<td>The child is breathing spontaneously and may have sleep/wake cycles. He may have non-purposeful or reflex movements of limbs or eyes. There is no evidence of ability to communicate verbally or non-verbally or to respond to commands.</td>
</tr>
</tbody>
</table>
| **3: Severe disability**  | (a) The child is at least intermittently able to move part of the body/eyes to command or make purposeful spontaneous movements; for example, confused child pulling at nasogastric tube, lashing out at carers, rolling over in bed. May be fully conscious and able to communicate but not yet able to carry out any self-care activities such as feeding.  
(b) Implies a continuing high level of dependency, but the child can assist in daily activities; for example, can feed self or walk with assistance or help to place items of clothing. Such a child is fully conscious but may still have a degree of post-traumatic amnesia. |
| **4: Moderate disability**| (a) The child is mostly independent but needs a degree of supervision/actual help for physical or behavioral problems. Such a child has overt problems; for example, a 12-year-old with moderate hemiplegia and dyspraxia insecure on stairs or needing help with dressing.  
(b) The child is age appropriately independent but has residual problems with learning/behavior or neurological sequelae affecting function. He probably should have special needs assistance but his special needs may not have been recognized/met. Children with symptoms of post-traumatic stress are likely to fall into this category. |
| **5: Good recovery**      | (a) This should only be assigned if the head injury has resulted in a new condition which does not interfere with the child's well-being and functioning; e.g.,  
  • Minor headaches not interfering with social or school functioning  
  • Abnormalities on brain scan without any detectable new problem  
  • Prophylactic anticonvulsants in the absence of clinical seizures  
  • Unusually scarring of face/head likely to need cosmetic surgery  
  • Mild neurological asymmetry, but no evidence of effect on function of limb. Includes isolated change in hand dominance in young child  
(b) Implies that the information available is that the child has made a complete recovery with no detectable sequelae from the head injury |

Paper I

During a 10-year period (2005–2015), 60 children ≤ 16 years of age, with severe TBI (GCSm ≤ 5), who were intubated and had ICP monitoring, were treated at the NICU. Twenty-one of these patients developed RICH despite surgical evacuation of mass lesions or decompressive craniectomy (DC) and received BCT. These 21 patients were included in this study. Demographic data and clinical information were retrieved from patient records. Physiological minute-by-minute data were retrieved from our database of digital monitoring recordings.

The following variables were studied: cause of injury; time from trauma to NICU; neurological status according to GCSm score 63 (Table 1) at admittance to the NICU and at departure; Rotterdam CT score 70,71 (Table 4) of initial brain CT scan; start and length of BCT; serum thiopental concentrations; dose of thiopental; side effects observed during BCT (infections, hepatocellular toxicity, and renal dysfunction); and deviations from goals. The patients were clinically characterized. The BCT management were explored, side-effects analyzed, and clinical outcome evaluated.

Table 4. Rotterdam Computed Tomography Classification 70,71 of traumatic brain injury. IVH: intraventricular hemorrhage, t-SAH: traumatic subarachnoid hemorrhage.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Cisterns</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Compressed</td>
<td>1</td>
</tr>
<tr>
<td>Absent</td>
<td>2</td>
</tr>
<tr>
<td>Midline Shift</td>
<td></td>
</tr>
<tr>
<td>Shift &lt; 5 mm</td>
<td>0</td>
</tr>
<tr>
<td>Shift &gt; 5 mm</td>
<td>1</td>
</tr>
<tr>
<td>Epidural mass lesion</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>0</td>
</tr>
<tr>
<td>Absent</td>
<td>1</td>
</tr>
<tr>
<td>IVH or t-SAH</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>Sum score</td>
<td>+1</td>
</tr>
</tbody>
</table>
Paper II

During 2007-2017, 72 children ≤17 years with TBI and GCSm ≤5 were treated at our NIC unit. Twenty-four (33%) of these patients received BCT due to RICH. In 17 of these children high resolution ICP data were recorded while in the remaining seven children only minute-by-minute data were collected or data were incomplete. In this study, the 17 children with high resolution data were included. All children received BCT for more than 24 hours.

The following clinical variables were studied: cause of injury; time from trauma to initiation of BCT; GCSm\(^{63}\) (Table 1) at admission to the NICU, and at departure; the Rotterdam CT score\(^{70,71}\) (Table 4) of initial brain CT scan; length of BCT, given doses of thiopental and serum-thiopental concentrations.

MAP, ICP, CPP and RAP index (Fig. 3) were analyzed at half hour periods before, during and after BCT: 1. The period just before bolus initiation of thiopental, 2. Between hour 5-5.5 after given bolus, 3. Between hour 10-10.5 after given bolus, 4. Between hour 24-24.5 after given bolus, and 5. A tapering period from when the serum thiopental concentration was below 100 until <30 was also studied (Fig. 5). The percentage of good monitoring time (%GMT) with ICP>20 mm Hg and ICP>25 mm Hg were analyzed during period 1 and the whole BCT period.

![Figure 5](image.png)

**Figure 5.** Timeline (h) of five periods that were studied. BCT: barbiturate coma treatment. RICH: refractory intracranial hypertension.

Paper III

During 2007-2018, 78 children ≤17 years with TBI and GCSm ≤5 were treated at our NIC unit. Fifty-seven children who had stored collected high resolution monitoring data were included in the study. Demographics and clinical information were retrieved from patient records and Uppsala Traumatic Brain Injury register\(^{69}\).

The following clinical variables were studied: demographics, cause of injury, the Rotterdam CT score\(^{70,71}\) (Table 4) of initial brain CT scan, GCSm\(^{63}\) (Table 1) on admission to and at departure from the NICU, BCT and/or DC.
The ICP and arterial blood pressure (ABP) waveform data were continuously recorded for each patient at a sampling rate of 100 Hz (high frequency) using the Odin software developed at Uppsala University and University of Edinburgh\textsuperscript{59,72}. PRx was calculated in Odin as a moving 5-min correlation of 10 sec averages of ICP and MAP\textsuperscript{50,60} (Fig. 1). CPPopt was calculated as the CPP with the lowest PRx during the previous 4 h period\textsuperscript{61} (Fig. 2). Deviations from CPPopt were denoted ΔCPPopt and calculated as the difference between actual CPP and CPPopt. ΔCPPopt is presented as percentage of good monitoring time (%GMT) with ΔCPPopt <-10, ±10 or >10, respectively. GMT is the remaining monitoring time after removing time gaps with missing data due to e.g., surgery and radiology. Mean values were calculated for ICP, CPP, PRx, CPPopt. Monitoring variables were analyzed for the whole monitoring period from the time of trauma (maximally 10 days) and for each day. The daily requirements for patient data contribution were GMT collected monitoring data >10% of the day.

**Paper IV**

All children ≤17 years, with severe TBI (defined as GCSm ≤5) admitted to the NIC unit between 2007-2020 were eligible for this pilot study. Among 82 eligible children, 61 had high resolution (100 Hz) monitoring data and 21 had CMD. Twenty-one children who had both high resolution monitoring data and CMD data were selected for this study. Demographics and clinical information were retrieved from patient records and Uppsala Traumatic Brain Injury register\textsuperscript{69}.

The following clinical variables were included: demographics, the Rotterdam CT score\textsuperscript{70,71} (Table 4) of initial brain CT scan, GCSm\textsuperscript{63} (Table 1) on admission and departure from the NICU, BCT and/or DC. Hourly means of CPP, PRx, CPPopt and ΔCPPopt were calculated and time-matched to the hourly collected CMD parameters lactate and LPR for each patient. ΔCPPopt is also presented as %GMT with ΔCPPopt <-10, ±10 or >10, respectively. Monitoring variables were analyzed from time of injury up to 10 days post-injury. No specific treatments for CMD disturbances were used. Instead, the CMD monitoring was used as an early warning system for emerging treatable secondary insults.

**Statistical analysis**

All data were transferred to SPSS v 27 (IBM) for statistical analysis. Differences were considered statistically significant if \( p<0.05 \).
Paper I - Descriptive statistics only.

Paper II - Non-parametric statistics. The Wilcoxon Signed Rank Test was used to analyze differences between the period just before bolus initiation of thiopental and each subsequent study period.

Paper III - The Shapiro-Wilk test confirmed normal distribution of waveform data in all periods and therefore parametric statistics were used. Continuous variables were described as mean (± 95% CI). Student’s t-test was used to assess differences between patients with favorable and unfavorable outcome. To adjust for the different ages of the children an ANCOVA was also performed with age as covariate. For the age analysis, the children were divided into two age groups. The age division ≤15/≥16 was chosen to get similar numbers of children and children with unfavorable outcome, respectively, in each group.

Paper IV - Histograms were used to visualize the distribution of CPP, PRx, CPPopt and ΔCPPopt. The time-matched hourly means of continuous monitoring variables and CMD parameters were presented as mean (95% CI) for the whole studied monitoring period. Based on the histogram frequency distribution of CPP and CPPopt, a cut-off at 70 mmHg was applied for dichotomization in order to compare results with CMD lactate and LPR. PRx was also dichotomized, with a cut-off at 0.1 according to the histogram distribution as well as to previous CPA studies using PRx in children with TBI. Non-parametric statistics were used, Mann-Whitney U test for dichotomized comparison and Kruskal-Wallis test with Bonferroni correction for trichotomized ΔCPPopt comparison.

Ethics

The studies were in compliance with ethical standards of the 1964 Helsinki declaration and its later amendments and approved by the Uppsala University Regional Ethical Review Board. Informed consent was obtained by the legal guardian of each participating patient.
Results, main findings

Paper I

The median age of the 21 children was 14 years (range 2–16 years). There were 12 boys and 9 girls, with a median weight of 58 kg (range 12–82 kg). At admission to the NIC unit, the median GCS score was 7 (range 4–8) and median GCSm score was 5 (range 2–5). Nine of the children had fixed dilated pupils at admission, 3 bilateral and 6 unilateral. Seven children showed focal motor deficits at admission. On the first CT scan of the brain the median Rotterdam CT score was 4 (range 4–5). The average time from accident to arrival at the initial local ICU was approximately 2.9 hours (range 0.5–9 hours). Three children underwent unilateral DC, 2 before thiopental onset, and 1 during thiopental treatment. Another 2 patients underwent bifrontal DC after BCT onset. Five other children had mass lesions evacuated prior to BCT.

The median time period from trauma to onset of BCT was 46 hours (range 4.7–197.5 hours). Nineteen children were treated with intravenous thiopental and received a median bolus at initiation of 5.5 mg/kg (range 2.3–15.2 mg/kg) followed by a median infusion rate of 5.5 mg/kg/h (range 4–8 mg/kg/h). Median duration of thiopental infusion was 107 hours (range 25–329 hours). Two children received thiopental as suppositories and had a mean bolus dose of 7.73 mg/kg followed by 1.43 mg/kg/h with suppositories at regular intervals. Median maximum serum thiopental for all children was 220 μmol/L (range 30–460 μmol/L). The onset of BCT resulted in lower ICP values, lower pulse amplitudes on the ICP curve, and decreased amount of A-waves.

At initiation of BCT the median sodium concentration was 141 mmol/L (range 132–148 mmol/L; >140 mmol/L in all except in two patients). The sodium concentration increased temporarily above 150 mmol/L in 5 patients during BCT. Blood samples did not show any clinically significant renal dysfunction or hepatocellular toxicity, except transiently in one patient. All of these parameters normalized by the end of the NIC period. All children required inotropic infusions during BCT to maintain sufficient MAP and prevent hypotension, and thereby also maintaining sufficient CPP.

Seventeen children were diagnosed with ventilator-associated pneumonia (verified by chest radiography) and treated with antibiotics. None of these
children developed severe respiratory problems. The average length of stay at
our NICU was 21 days (range 11–44 days). At discharge, 11 children had been
extubated with a mean intubation period of 16 days (range 10–28 days) and 9
children had a tracheostomy due to insufficient neurological recovery (4 still
in need of mechanical ventilation). The clinical outcome is presented in Figure
6.

Figure 6. Outcome 12 months after TBI according KOSCHI66,67 (Table 3).

Paper II

The median age of the 17 children studied was 15 years (range 6-17) and me-
dian weight 59 kg (range 22-82). At admittance to Uppsala, the median GCS
was 7 (range 3-8) and median GCSm was 5 (range 2-5). Median Rotterdam
classification of the first brain CT was 4 (range 3-5).

DC was performed in seven children; two acutely before BCT, one acutely at
start of BCT and the remaining four during BCT. Three of the seven children
had hematoma evacuation at the same time as the DC; one before BCT, one
at start of BCT, one in BCT period 5. In another four children a hematoma
was evacuated prior to BCT without DC.

Median ICP was 22 (IQR 20-25) in the half hour period before onset of BCT
and 16 (IQR 11-20) in the half hour period 5 h later (p=0.011) (Fig. 7). The
median RAP index was in the half hour period before onset of BCT 0.6 (IQR
0.1-0.7), in the half hour period 5 h later 0.3 (IQR 0.1-0.7) (p=0.331) (Fig.7)
and in the whole BCT period 0.3 (IQR 0.2-0.4) (p=0.004) (Fig. 8). Median
MAP decreased after initiation of BCT (Fig. 7). Median CPP remained more
or less unchanged; just above 60 mm Hg before onset of BCT and during the
first 24 hours of BCT, and slightly increased during the tapering period (Fig.
7).
Looking at proportions of time spent above the defined thresholds, ICP was >20 mmHg in 70% of the time and >25 mmHg in 33% of the time in period 1 before BCT. There were significantly lower values for the whole BCT period; ICP >20 mmHg 7% of the time (p=0.002) and ICP >25 mmHg 0.5% of the time (p=0.002) (Fig. 8).
Figure 8. Proportion of ICP over 20 mm Hg (A), proportion of ICP over 25 mm Hg (B) and median RAP index (C) for half an hour before onset of barbiturate coma treatment (BCT) and for the whole BCT period.

Paper III

Median age of the 57 children was 15 years (range 0.5-17). There were 41 males and 16 females. Median GCSm on admission was 5 (range 2-5). Median Rotterdam CT classification of the first brain scan was 4 (range 3-5). All children were mechanically ventilated and had intracranial pressure monitoring. Twenty-eight children received one, two or three of the following interventions: barbiturate coma treatment (n=17), decompressive craniectomy (n=11) and hematoma evacuation (n=19). At discharge from NIC, median GCSm was 6 (range 1-6). Forty-nine patients (86%) had favorable outcome (GOS 4-5) and 8 (14%) unfavorable (GOS 1-3) 6 months after trauma.

Mean ICP for all children was 12.0 mmHg (±1.1) (Table 5). There was no significant difference in mean ICP between the favorable outcome group and the unfavorable outcome group (Table 5). Mean CPP was 69.7 (±1.6) and mean CPPopt 69.2 (±2.3) for all children (Table 5). There were no significant differences in mean CPP or CPPopt between the favorable and unfavorable outcome groups (Table 5). Mean PRx for all children was -0.02 (±0.04) (Table 5). Mean PRx in children with favorable outcome was -0.03 (±0.04) and 0.07 (±0.14) in children with unfavorable outcome (p=0.052, t-test) (Table 5 and Fig. 9). When the analysis was adjusted for the different ages of the children in the ANCOVA (age as covariate) the difference became statistically significant (p=0.023, Table 5). For all children the mean %GMT with ΔCPPopt < -10 was 33.4 (±3.9), with ΔCPPopt ≥10 41.5 (±2.8) and ΔCPPopt >10 24.9 (±2.6), respectively (Table 5). There were no significant differences in mean ΔCPPopt between the two outcome groups (Table 5).
When the children were divided into two age groups, mean PRx in younger children (≤15 years) was significantly lower for those with favorable outcome (PRx -0.02 ±0.04) compared to those with unfavorable outcome (PRx 0.12 ±0.16) (p=0.016) (Table 5 and Fig. 9). There was no significant difference in PRx amongst the older children (≥16 years) related to outcome (Table 5 and Fig. 9). Younger children with favorable outcome had significantly lower %GMT with ΔCPPopt< -10 (31.9% ±4.9) compared to those with unfavorable outcome (48.3% ±32.3) (p=0.038) (Table 5). No significant differences regarding %GMT ΔCPPopt ±10 and ΔCPPopt >10 were seen between the two outcome groups in either age group (Table 5).

**Table 5.** Clinical outcome (Favorable/Unfavorable) and mean monitoring values whole monitoring period (± 95% CI) for ICP, CPP, PRx, CPPopt, ΔCPPopt <-10 (%GMT), ΔCPPopt ±10 (%GMT), ΔCPPopt >10 (%GMT). Monitoring data and outcome are presented for all children and children ≤15 years and ≥16 years using t-test. P-values for all children (non-dichotomized) using ANCOVA are presented in last column. N/A = not applicable.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Favorable</th>
<th>Unfavorable</th>
<th>p t-test</th>
<th>p ANCOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>57 (100%)</td>
<td>49 (86%)</td>
<td>8 (14%)</td>
<td>0.052</td>
<td>0.023</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td>12.0 (±1.1)</td>
<td>11.7 (±1.3)</td>
<td>13.9 (±1.6)</td>
<td>0.165</td>
<td>0.194</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>69.7 (±1.6)</td>
<td>69.8 (±1.8)</td>
<td>69.5 (±5.5)</td>
<td>0.902</td>
<td>0.556</td>
</tr>
<tr>
<td>PRx</td>
<td>-0.02 (±0.04)</td>
<td>-0.03 (±0.04)</td>
<td>0.07 (±0.14)</td>
<td>0.052</td>
<td>0.023</td>
</tr>
<tr>
<td>CPPopt (mmHg)</td>
<td>69.2 (±2.3)</td>
<td>68.9 (±2.6)</td>
<td>71.0 (±4.7)</td>
<td>0.527</td>
<td>0.737</td>
</tr>
<tr>
<td>ΔCPPopt &lt;10%</td>
<td>33.4 (±3.9)</td>
<td>32.9 (±3.9)</td>
<td>36.6 (±16.9)</td>
<td>0.507</td>
<td>0.360</td>
</tr>
<tr>
<td>ΔCPPopt ±10%</td>
<td>41.5 (±2.8)</td>
<td>41.7 (±2.9)</td>
<td>40.0 (±10.3)</td>
<td>0.676</td>
<td>0.470</td>
</tr>
<tr>
<td>ΔCPPopt &gt;10%</td>
<td>24.9 (±2.6)</td>
<td>25.2 (±2.8)</td>
<td>23.1 (±8.7)</td>
<td>0.582</td>
<td>0.863</td>
</tr>
<tr>
<td>Patients&lt;15yrs.</td>
<td>35 (61%)</td>
<td>31 (89%)</td>
<td>4 (11%)</td>
<td>0.078</td>
<td>N/A</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td>11.7 (±1.3)</td>
<td>11.3 (±1.4)</td>
<td>14.7 (±2.0)</td>
<td>0.302</td>
<td>N/A</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>69.2 (±2.4)</td>
<td>69.6 (±2.5)</td>
<td>65.8 (±9.9)</td>
<td>0.12 (±0.16)</td>
<td>0.016</td>
</tr>
<tr>
<td>PRx</td>
<td>-0.01 (±0.04)</td>
<td>-0.02 (±0.04)</td>
<td>0.12 (±0.16)</td>
<td>0.016</td>
<td>N/A</td>
</tr>
<tr>
<td>CPPopt (mm Hg)</td>
<td>69.1 (±3.1)</td>
<td>68.6 (±3.4)</td>
<td>72.9 (±7.9)</td>
<td>0.377</td>
<td>N/A</td>
</tr>
<tr>
<td>ΔCPPopt &lt;10%</td>
<td>33.8 (±5.1)</td>
<td>31.9 (±4.9)</td>
<td>48.3 (±32.3)</td>
<td>0.038</td>
<td>N/A</td>
</tr>
<tr>
<td>ΔCPPopt ±10%</td>
<td>42.3 (±4.0)</td>
<td>43.3 (±4.3)</td>
<td>34.7 (±15.6)</td>
<td>0.171</td>
<td>N/A</td>
</tr>
<tr>
<td>ΔCPPopt &gt;10%</td>
<td>23.7 (±3.2)</td>
<td>24.6 (±3.0)</td>
<td>16.8 (±16.9)</td>
<td>0.109</td>
<td>N/A</td>
</tr>
<tr>
<td>Patients&gt;16yrs.</td>
<td>22 (39%)</td>
<td>18 (82%)</td>
<td>4 (18%)</td>
<td>0.797</td>
<td>N/A</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td>12.5 (±2.2)</td>
<td>12.4 (±2.7)</td>
<td>13.1 (±3.5)</td>
<td>0.268</td>
<td>N/A</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>70.6 (±2.3)</td>
<td>70.0 (±2.5)</td>
<td>73.1 (±8.2)</td>
<td>0.528</td>
<td>N/A</td>
</tr>
<tr>
<td>PRx</td>
<td>-0.03 (±0.15)</td>
<td>-0.04 (±0.08)</td>
<td>0.02 (±0.34)</td>
<td>0.944</td>
<td>N/A</td>
</tr>
<tr>
<td>CPPopt (mm Hg)</td>
<td>69.4 (±3.6)</td>
<td>69.4 (±4.3)</td>
<td>69.1 (±9.8)</td>
<td>0.231</td>
<td>N/A</td>
</tr>
<tr>
<td>ΔCPPopt &lt;10%</td>
<td>32.8 (±6.3)</td>
<td>34.5 (±7.0)</td>
<td>24.9 (±21.5)</td>
<td>0.152</td>
<td>N/A</td>
</tr>
<tr>
<td>ΔCPPopt ±10%</td>
<td>40.1 (±3.5)</td>
<td>39.0 (±3.2)</td>
<td>45.4 (±21.5)</td>
<td>0.604</td>
<td>N/A</td>
</tr>
<tr>
<td>ΔCPPopt &gt;10%</td>
<td>26.9 (±4.7)</td>
<td>26.4 (±5.7)</td>
<td>29.5 (±9.2)</td>
<td>0.604</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Figure 9. Pressure autoregulation during the whole monitoring time period presented as pressure reactivity index (mean PRx±95% CI) for favorable (transparent bars) and unfavorable (grey bars) outcome groups in children of all ages (ANCOVA), children ≤15 years (t-test) and children ≥16 years (t-test), respectively.

PRx showed different temporal courses for the outcome groups (Fig. 10). In the favorable outcome group, PRx had a temporal decreasing trend the first five days from 0.05 to -0.07, increased day 6 and 7 to 0.02 and decreased thereafter again the following three days to -0.05. The unfavorable group showed an opposite PRx pattern with an increase from 0.00 to 0.11 the first five days and then stayed elevated around that level. Looking at the temporal trend for CPPopt, it appeared to be higher in the unfavorable group from day 6, the time period when CPA is most impaired.

Figure 10. Temporal monitoring data: PRx for all children and divided in favorable and unfavorable outcome groups (mean ± 95% CI each day of the monitoring period).
Paper IV

The study included a total of 21 children with median age 16 years (range 8-17), median GCSm 5 (range 2-5) on admission and median Rotterdam CT classification 4 (range 3-5) of the first brain CT. All children were mechanically ventilated and had intracranial pressure monitoring. Seven children received one, two or three of the following interventions: barbiturate coma treatment (n=5), decompressive craniectomy (n=5) and hematoma evacuation (n=3). Median GCSm was 6 (range 1-6) at discharge from NIC. Median GOS six months after trauma was 4 (range 1-5) and 13 children were assessed to have favorable outcome (GOS 4-5) and 8 unfavorable (GOS 1-3).

The time matched cerebral monitoring data and CMD data are presented in Table 6. There were significantly higher values when CPP ≥70 mmHg than when CPP <70 mmHg both for lactate (4.29 mM [95% CI 4.17 to 4.40] vs 4.02 mM [95% CI 3.92 to 4.13], p = 0.010) and LPR (27.86 [95% CI 27.30 to 28.43] vs 26.22 [95% CI 25.73 to 26.71], p = <0.001) (Fig. 11).

There were significant higher values when PRx ≥ 0.1 than when PRx <0.1 both for lactate (4.57 mM [95% CI 4.41 to 4.72] vs 4.00 mM [95% CI 3.91 to 4.08, p = < 0.001) and LPR (28.33 [95% CI 27.55 to 29.10] vs 26.54 [95% CI 26.12 to 26.97], p = <0.001) (Fig. 12).

CPPopt showed no significant differences in lactate levels between CPPopt >70 mm Hg and < 70 mm Hg (4.13 mM [95% CI 3.99 to 4.26] vs 4.20 [95% CI 4.06 to 4.34], p = 0.162) (Table 5). LPR was significantly lower when CPPopt ≥70 mmHg than when CPPopt < 70 mmHg (27.48 [95% CI 26.73 to 28.24] vs 27.83 [95% CI 27.17 to 28.49], p = 0.012) (Table 6).

There were significantly higher values during the periods of GMT when ΔCPPopt >10 than when ΔCPPopt <–10 for lactate (4.39 mM [95% CI 4.20 to 4.58 vs (4.10 mM [95% CI 3.90 to 4.30], p = 0.026) and LPR (28.47 [95% CI 27.45 to 29.48] vs 26.90 [95% CI 25.77 to 28.04], p= 0.002) (Table 6 and Fig. 13).
Table 6. CMD Lactate (mM) and LPR mean values (95% CI) presented by dichotomized CPP, PRx and CPPopt, respectively, and by ΔCPPopt, ΔCPPopt <-10, ΔCPPopt ±10 and ΔCPPopt >10 (%GMT).

<table>
<thead>
<tr>
<th></th>
<th>Lactate, mM</th>
<th>LPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPP &lt; 70, mm Hg</td>
<td>4.02 (3.92 to 4.13)</td>
<td>26.22 (25.73 to 26.71)</td>
</tr>
<tr>
<td>CPP ≥ 70, mm Hg</td>
<td>4.29 (4.17 to 4.40)</td>
<td>27.86 (27.30 to 28.43)</td>
</tr>
<tr>
<td>p</td>
<td>0.010</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRx &lt; 0.1</td>
<td>4.00 (3.91 to 4.08)</td>
<td>26.54 (26.12 to 26.97)</td>
</tr>
<tr>
<td>PRx ≥ 0.1</td>
<td>4.57 (4.41 to 4.72)</td>
<td>28.33 (27.55 to 29.10)</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPPopt &lt; 70, mm Hg</td>
<td>4.20 (4.06 to 4.34)</td>
<td>27.83 (27.17 to 28.49)</td>
</tr>
<tr>
<td>CPPopt ≥ 70, mm Hg</td>
<td>4.13 (3.99 to 4.26)</td>
<td>27.48 (26.73 to 28.24)</td>
</tr>
<tr>
<td>p</td>
<td>0.162</td>
<td>0.012</td>
</tr>
<tr>
<td>ΔCPPopt &lt;-10</td>
<td>4.10 (3.90 to 4.30)</td>
<td>26.90 (25.77 to 28.04)</td>
</tr>
<tr>
<td>p (a vs b)</td>
<td>1.00</td>
<td>0.060</td>
</tr>
<tr>
<td>p (a vs c)</td>
<td>0.026</td>
<td>0.002</td>
</tr>
<tr>
<td>ΔCPPopt ±10</td>
<td>4.08 (3.94 to 4.22)</td>
<td>27.60 (26.91 to 28.29)</td>
</tr>
<tr>
<td>p (b vs a)</td>
<td>1.00</td>
<td>0.060</td>
</tr>
<tr>
<td>p (b vs c)</td>
<td>0.003</td>
<td>0.248</td>
</tr>
<tr>
<td>ΔCPPopt &gt;10</td>
<td>4.39 (4.20 to 4.58)</td>
<td>28.47 (27.45 to 29.48)</td>
</tr>
<tr>
<td>p (c vs a)</td>
<td>0.026</td>
<td>0.002</td>
</tr>
<tr>
<td>p (c vs b)</td>
<td>0.003</td>
<td>0.248</td>
</tr>
</tbody>
</table>

Figure 11. Lactate (mM) and LPR mean values (95% CI) presented by dichotomized CPP.
Figure 12. Lactate (mM) and LPR mean values (95% CI) presented by dichotomized PRx.

Figure 13. Lactate (mM) and LPR mean values (95% CI) presented by ΔCPPopt < –10, ΔCPPopt ±10 and ΔCPPopt > 10.
Discussion

Specialized NIC with multimodality monitoring and secondary insult prevention is of crucial importance for favorable clinical outcome following moderate and severe TBI. TBI is among the most common causes of death and acquired disability during childhood. The management guidelines for children are usually mainly extrapolated from adults. At present, studies of BCT of RICH and studies of CPA are limited in children. The focus of this thesis was therefore to improve the state of knowledge concerning these topics for the pediatric TBI population.

Barbiturate coma treatment (Papers I and II)

Analysis of long-term clinical outcome at 1-year in children receiving BCT as last tier treatment for RICH showed a median GOS score of 5 and a median KOSCHI score of 4a. Thus, it is possible to achieve relatively good clinical outcome using BCT in this subgroup of children with severe TBI and RICH. Furthermore, in many cases BCT was sufficient to treat RICH and thereby a surgical procedure of DC and its potential complications avoided, as well as the need for cranioplasty, also with risk of complications.

When the occurrence of BCT-related complications was investigated, no serious medical events were observed. In the past, severe treatment-related complications contributed to increased mortality and unfavorable outcome, which negatively influenced overall outcome. Modern NIC probably provides better conditions for successful BCT and long-term experience of BCT is probably also of importance.

The results give an indication of the increased safety that a modern NICU provides even if it is difficult to identify any specific factor of importance. Instead, protocol-based treatment strategies, imaging, computer-based multimodality monitoring, and the focus on avoiding all kinds of secondary insults have all together probably contributed to this level of safety. Another important contributing factor in achieving high quality of NIC, is probably to have staff specialized in NIC with high competence level among all types of
staff so that the implementation of advanced neuromonitoring, secondary insult prevention and standardized, respectively, care can be maintained\textsuperscript{4,64}.

The major findings when the effect of BCT on intracranial and systemic physiological variables were studied were that both ICP and RAP index improved substantially shortly after initiation of BCT with a slight decrease of MAP but virtually unchanged CPP. During the last half hour before start of BCT, median ICP was 22 mmHg and the median proportion of monitoring time with ICP $> 20$ mmHg and ICP $> 25$ mmHg was $\sim 70\%$ and $\sim 30\%$, respectively, for that period of time. This indicates that there was a clear indication for escalating the treatment and start BCT, which was further supported by a median RAP index of 0.6 the half hour before start of BCT. The severity of RICH was also underlined by the fact that several children already had been operated with evacuation of mass lesion and DC before initiation of BCT.

A more detailed analysis of the temporal effects of BCT on intracranial pressure dynamics revealed that median ICP and median RAP index was clearly reduced in period 2 five hours after thiopental bolus. The improvement in ICP and RAP index were also maintained in the later study periods. The BCT effects were clear when the $\%$GMT the half hour before BCT was $70\%$ for ICP $> 20$ mm Hg and $35\%$ for ICP $> 25$ mm Hg to be compared with $7\%$ and $0.5\%$, respectively, for the whole BCT period.

The early effect of BCT on ICP is usually explained by the coupling between cerebral metabolism and CBF; the decreased cerebral metabolism caused by the BCT lowers CBF by vasoconstriction which reduces the cerebral blood volume and thereby also ICP\textsuperscript{28}. Barbiturates may also improve an ischemic situation, since the decreased metabolism reduces the metabolic oxygen demand\textsuperscript{75}, which untreated may lead to irreversible brain injuries and subsequent brain edema. In addition, barbiturates may also prevent secondary injury mechanisms, e.g. glutamate excitotoxicity\textsuperscript{27}. On the other hand, BCT has been associated with severe side-effects which may lead to multiorgan failure\textsuperscript{12,76}. However, the complications are strongly related to the serum concentration. The risk may be reduced if higher serum concentrations ($> 300 \mu$mol/L) are avoided\textsuperscript{14}, as in our ICP-oriented treatment strategy. Furthermore, when there are indications of emerging severe complications these can be prevented if BCT is stopped and DC performed instead. To summarize, the results of the present study of BCT in children\textsuperscript{32,77} indicate that BCT reduces ICP effectively and that favorable results can be achieved.
Cerebral pressure autoregulation and Optimal CPP (Papers III and IV)

For the whole group of children including all ages, a significantly lower PRx (better preserved CPA) was found in the favorable outcome group (p=0.023). In the subgroup analysis of different age groups, this finding was statistically significant in children ≤15 years (p=0.016), but not in children ≥16 years (p=0.528). The influence of CPA status on outcome in children ≤15 years was further supported by the finding in those children that lower %GMT with ΔCPPopt < -10 was significantly associated to favorable outcome (p=0.038), but not in the older age group. No associations were found to outcome regarding the proportions of time with %GMT ΔCPPopt within ±10 and ΔCPPopt >10, indicating that it is more dangerous with actual CPP below the optimal level than above, especially in the younger age. Hence, CPA status may have strongest effect on outcome in children ≤15 years of age and it may be most important in that age group to keep CPP close to or above CPPopt. However, ≤15 years should not be considered as an exact discriminating age limit since that limit was chosen for statistical reasons. Unfortunately, our patient material did not permit subgroup analysis with smaller age spans.

Despite our ICP-oriented treatment protocol, the findings of this study in children exhibit a mean CPP as high as close to 70 mm Hg. The calculated mean CPPopt was also at the same level. However, when looking at ΔCPPopt, the proportion of monitoring time with CPP close to CPPopt was only around 42% and CPP was below CPPopt in around 33% and above in 25% of the monitoring time, respectively. This finding was also similar between the age groups. It is apparent that using a fixed lower CPP thresholds results in a large proportion of monitoring time deviating from CPPopt, although our results indicate that deviations below CPPopt might be most important to avoid and especially in the group of children ≤15 years of age.

ICP and CPP did not show any relation to outcome. This finding should not be interpreted as those parameters are unimportant to treat. The explanation is rather that those factors were thoroughly managed according to targeted goals (unlike CPPopt) and severe deviations avoided, especially very high ICP and very low CPP.

Regarding temporal trends of PRx, the strongest impression was that PRx appeared to reach a level of impaired CPA in the unfavorable outcome group after a few days and that this differed compared to the favorable outcome group from that time point onward. This is, however, not proven statistically and deserves further studying in larger patient materials. The impression was also that CPPopt was higher in the unfavorable group during the same time...
period, but no significant differences were found there either. Unfortunately, regarding the temporal course, the number of patients did not permit any age subgroup analysis for the different physiological parameters, which would have been interesting. Altogether, the results substantiate the findings in earlier studies that impaired CPA is related to poor outcome\textsuperscript{17,45-49} and that CPP close to or above CPP\textsubscript{opt} is associated with favorable outcome\textsuperscript{46,47,49}.

One way of evaluating the clinical significance of disturbed CPA and the potential of using CPP\textsubscript{opt} for guidance of CPP treatment is to study those measures in relation to clinical outcome. Clinical outcome may however be influence by other factors than pathophysiology and management during NIC, e.g. rehabilitation efforts, social network and socioeconomic factors. A complementary way of evaluating CPA and CPP\textsubscript{opt} is to use a surrogate end point such as the chemistry of the brain which may be monitored by using CMD. CMD provides a possibility to analyze the chemical content of the interstitial fluid in the brain, i.e. it enables measurements of for example metabolites, excitotoxic amino acids and biomarkers. We chose to analyze lactate and LPR in this study to obtain information about the cerebral metabolism and the intracellular redox state of the brain\textsuperscript{52}. Lactate and foremost the lactate/pyruvate ratio (LPR) are the most robust biochemical markers of ischemia reflecting secondary brain injury\textsuperscript{78,79}.

When the metabolic state of the brain was studied using CMD, the integrity of CPA (PRx), and deviations from CPP\textsubscript{opt} (ΔCPP\textsubscript{opt}) were related to the metabolic redox status. Both lactate and LPR were significantly higher when CPP and PRx were higher, although the levels of lactate and LPR did not reach very high levels when compared to estimated normal values in adults\textsuperscript{80}. The results give additional support for the role of PRx as a surrogate marker of CPA and that impaired CPA is negative for the brain. Furthermore, the results also indicate that higher CPP is unfavorable for the brain. A negative influence of low CPP was not seen, but it is important to emphasize that very low CPP rarely occurred. When discussing the influence of CPP levels on cerebral metabolism it is also important to consider CPP\textsubscript{opt} and the impact of deviations from CPP\textsubscript{opt}. It is possible that the observed relation between the actual CPP levels and the microdialysis levels to some extent may be explained by deviations between actual CPP and CPP\textsubscript{opt}.

No significant lactate and LPR differences were seen between CPP\textsubscript{opt} ≥ 70 or < 70 mmHg, which was expected and in line with our previous findings that CPP\textsubscript{opt} was not related to outcome\textsuperscript{73}. Interestingly, when ΔCPP\textsubscript{opt} was >10 both lactate and LPR were significantly higher. It is therefore possible that this partly may be the reason behind why CPP was found to be associated with higher lactate and LPR. A possible mechanism may be that hyper-perfusion occurs when actual CPP is above the upper limit of pressure autoregulation,
which may lead to aggravation of the brain injury. In the previous study deviations from CPPopt did not seem to influence outcome significantly when we looked at all included children while a larger proportion of GMT with ΔCPPopt < –10 in smaller children was associated with less favorable outcome. These discrepancies may have several explanations. Fewer younger children were included in this study and it is possible that younger children are more sensitive to CPP below CPPopt. Furthermore, even if the proportion of GMT with ΔCPPopt > 10 was similar in the two studies the degree of deviation from CPPopt may have been different. Finally, the comparison between the two studies needs to be cautious and it is therefore important to emphasize that clinical outcome and cerebral metabolism are different outcome variables and one cannot anticipate for sure that those are completely interrelated.

Even if normal/abnormal ranges for lactate and LPR have not been established in the pediatric population one can assume that the ranges are similar as in adults. Earlier studies in adults with TBI have used CMD to assess the safe lower limit of CPP suggesting that management might be individualized. This is a potential application of CMD in pediatric TBI also, although we could not identify any critical thresholds of CPP in this study, possibly because CPP was never critically low.

Limitations

The major limitation of these studies were the limited number of patients included and the fact that very few young children were studied. Another limitation was that the studies were retrospective even though the data was prospectively collected. Despite the limitations, valuable knowledge was obtained, taking into account the sparse published results on the use of barbiturates in children with RICH in a modern NIC setting as well as the limited number of published studies concerning CPA and CPPopt in pediatric TBI using high resolution data, and especially in combination with CMD.

Concluding remarks

The modern NIC setting with computerized multimodality monitoring and systems for data collection provides a unique platform for explorative research. Valuable information concerning pathophysiology and treatment effects may be obtained in children with TBI, despite the small patient population. Further studies in this field are encouraged.
Conclusions

Paper I
BCT due to RICH in children with severe TBI can be an effective means of lowering ICP without causing concomitant severe side effects when used in a modern NICU setting. The treatment strategy resulted in relatively good long-term outcome.

Paper II
BCT due to RICH in children with severe TBI reduces ICP significantly and quickly, and improves intracranial compensatory reserve (RAP-index), with maintained level of CPP.

Paper III
Impaired CPA (PRx) is related to poor outcome, particularly in children ≤15 years of age. In that age group, actual CPP below the optimal CPP level was significantly associated with unfavorable outcome, while levels close or above CPPopt was unrelated to outcome. Temporal analysis indicated that CPA (PRx) was higher (more impaired CPA) and CPPopt was higher in the unfavorable outcome group than in the favorable outcome group after a few days, although those findings were not significant. CPPopt appeared to be higher when CPA is most impaired.

Paper IV
Higher levels of CMD lactate and LPR in children with severe TBI were related to disturbed CPA (higher PRx). Actual CPP levels ≥70 mmHg and CPP above CPPopt were associated with increased lactate and LPR. It is likely that higher CPP not always per se is harmful, but rather when CPP is above the upper limit of pressure autoregulation. The findings indicate that CPPopt guided CPP management may have potential, but further studies are required.
Bakgrund

Behandlingsrutinerna för barn med THS bygger till stor del på kunskap från vuxna patienter trots att det finns olika anatomiska och fysiologiska skillnader vilket måste beaktas vid neurointensivvård av barn med THS. Barn har till exempel relativt större huvud, tunnare kranium och rörligare nacke. Barn har också trängre förhållanden intrakraniellt på grund av en relativt större hjärna och mindre volym cerebrospinalvätska vilket gör att ICP ökar redan vid mindre intrakraniella blödningar eller hjärnvullnad. Barn har också lägre blodtryck normalt vilket gör att målnivåerna för CPP skiljer sig från vuxna. Med tanke på dessa aspekter så är det ett stort behov av mer studier specifikt på barn med THS. Modern neurointensivvård med datoriserade övervakningssystem där data kan sparas erbjuder en unik möjlighet att studera effekten av olika behandlingar och komplexa mekanismer i efterhand.

Erfarenheten av att söva THS patienter med barbiturater till djupt coma för att behandla högt ICP när enkla behandlingsåtgärder inte hjälper kommer främst

Ett annat viktigt område att studera på barn som utforskas på vuxna är möjligheten att kunna individualisera CPP/blodtrycks-behandlingen utifrån patientens förmåga att automatiskt reglera hjärtans blodflöde i relation till svängningar i blodtrycket. Denna regleringsmekanism kallas tryckautoreglering och kan vara störd vid THS. Det är möjligt att patienter med störd tryckautoreglering ska behandlas annorlunda. Insamlade övervakningsdata från neurointensivvården kan användas för att räkna ut olika surrogat-mått (baserade på ICP och blodtryck) vad gäller hur bra autoregulationen fungerar (PRx), intrakraniella kompensatoriska volymsreserven (RAP-index) samt optimalt CPP (CPPopt).

Målen med avhandlingen
Målsättningen var att studera barbiturat-koma behandling på grund av terapiresistent högt ICP (Delarbete I och II) respektive tryckautoregleringen (Delarbete III och IV) hos barn med THS med förhoppningen att kunna förbättra neurointensivvården för denna grupp av patienter på sikt och därigenom förbättra behandlingsresultaten.

Resultat och Diskussion
I Delarbete I studerades 21 barn med THS där samtliga behandlades med barbiturat-koma behandling på grund av terapiresistent högt ICP. Syftet var att i en modern neurointensivvårdsmiljö utvärdera behandlingsresultatet och förekomsten av komplikationer relaterade till behandlingen. Resultatet visade att behandling med barbiturat-koma på ett effektivt sätt sänkte ICP utan svåra komplikationer. Därmed behövdes skallbenet i många fall aldrig opereras bort (decompressiv kraniotomi) för att sänka ICP. Uppföljning visade relativt bra behandlingsresultat för denna grupp av patienter där 13/21 uppvisade normal funktionsnivå. Behandling med barbiturat-koma för att sänka terapiresistent högt ICP kan således vara ett effektivt behandlingsalternativ på barn med THS i sådana situationer.

I Delarbete II ingick 17 barn med THS som behandlades med barbiturat-koma på grund av terapiresistent ICP. Insamlade högupplösta (100 Hz) övervakningsdata från neurointensivvården analyserades med syfte att evaluerar effekten av barbiturat-koma på ICP, blodtryck, CPP och intrakraniell
kompensatorisk volymsreserv (RAP-index). Resultaten visade att behandling med barbiturat-koma gav en snabb signifikant sänkning av ICP och sänkning av RAP-index (förbättrad kompensatorisk volym-reserv) utan att CPP minskade. Sammanfattningsvis visar resultaten från de detaljerade analyserna av övervakningsdata att barbiturat-koma effektivt förbättrar den intrakraniella tryck-volym-situationen.

I Delarbete III analyserades högupplösta (100 Hz) övervakningsdata från 57 barn med THS som vårdats på neurointensivvårdsavdelningen. Syftet var att övergripande kartlägga förmågan till tryckautoreglering (PRx), uppmätta CPP-nivåer och kalkylerade optimala CPP-nivåer (CPPopt) samt avvikelser från CPPopt (ΔCPPopt), och mer detaljerat analysera dessa faktorers relationer till uppföljningsresultatet och hur de varierade över tid. Resultaten visade att försämrad tryckautoreglering var associerat med sämre uppföljningsresultat, särskilt hos barn ≤15 år. Stor andel av tiden med CPP under kalkylerat CPPopt (lägt ΔCPPopt) hos barn ≤15 år visade signifikant samband med sämre behandlingsresultatet, medan CPP nivåer nära eller över CPPopt inte visade ett sådant samband. CPPopt verkade vara högre i perioder när tryckautoregleringen fungerade sämst. Sammanfattningsvis talar resultaten för att det skulle kunna vara fördelaktigt att styra CPP/blodtrycks-behandlingen utifrån förmågan till tryckautoreglering även på barn med THS.

I Delarbete IV ingick 21 barn med THS som hade haft intracerebral mikrodialys för kontinuerlig kemisk övervakning av hjärnan under neurointensivvården och från vilka det fanns högupplösta (100 Hz) övervakningsdata från kontinuerliga tryckmätningarna. För att ytterligare värdera potentialen för att styra CPP/blodtrycks-behandlingen efter tryckautoregleringen relaterades nivåerna för ischemiska markörer i mikrodialysaten (laktat och laktat/pyruvat-kvoten) till förmågan att tryckautoreglera (PRx), CPP och CPPopt samt avvikelser från CPPopt (ΔCPPopt). Högre nivåer för laktat och hög laktat/pyruvat-kvot var associerat med försämrad autoreglering, CPP nivåer ≥70 mmHg och aktuellt CPP högre än CPPopt (högt ΔCPPopt). Resultaten talar för att CPP-nivåer som överskrider nivån för fungerande tryckautoreglering kan vara skadliga. Inget samband fanns med låga CPP under CPPopt men detta kan förklaras av att mycket lågt CPP var mycket ovanligt. Sammanfattningsvis indikerar resultaten även i denna studie att det skulle kunna vara fördelaktigt att styra CPP/blodtrycks-behandlingen utifrån förmågan till tryckautoreglering på barn med THS.

Avslutande kommentar
Modern neurointensivvård med datoriserade övervakningssystem och system för att spara övervakningsdata erbjuder en unik plattform för avancerad klinisk forskning. Patofysiologiska mekanismer och effekten av olika behandlingsinsatser kan studeras, vilket kan leda till nya behandlingskoncept.
Värdefulla resultat kan fås fram utan att mycket stora patientserier krävs. Med tanken på de anatomiska och fysiologiska skillnaderna mellan barn och vuxna förefaller det synnerligen angeläget att utnyttja den forskningsfacilitet som neurointensivvården erbjuder för barn med THS för att bättre underbygga och optimera behandlingsriktlinjerna för denna grupp i framtiden.
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