UMEÅ UNIVERSITY MEDICAL DISSERTATIONS

On Severe Traumatic Brain Injury

Aspects of an Intra Cranial Pressure-Targeted Therapy
Based on the Lund Concept

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Abstract

Severe Traumatic Brain Injury (sTBI) is a major cause of mortality and morbidity. At the Department of Neurosurgery Umeå University Hospital subjects with sTBI are treated with an intracranial pressure (ICP) guided therapy based on physiological principles, aiming to optimise the microcirculation of the brain so avoiding secondary brain injuries. The investigations in this thesis are unique in the sense that all patients with sTBI were treated according to the guidelines of an ICP targeted therapy based on the "Lund concept".

As the treatment is based on normalisation of the ICP, the accuracy and reliability of the measuring device is of outmost importance. Therefore the accuracy, drift, and complications related to the measuring device was prospectively studied (n=128). The drift was 0,9 ± 0,2 mmHg during a mean of 7,2 ± 0,4 days and the accuracy high. No clinical significant complications were noted.

In 1997 uni- or bilateral decompressive hemi-craniectomy (DC) was introduced into the treatment guidelines. The effect of DC on the ICP and outcome was retrospectively analysed for subjects with sTBI treated 1998-2001. In the subjects who underwent DC the ICP was 36,4 mmHg immediately before and 12,6 mmHg immediately after the DC. The ICP then levelled out at just above 20 mmHg. The ICP was significant lower during the 72 hours following DC. The outcome did not differ between subjects who had undergone DC or not.

Subclinical electroencephalographic seizures and status epilepticus have been reported to be common in subjects treated for traumatic brain injury (TBI). This can negatively influence the outcome giving rise to secondary brain injuries. The occurrence of seizures in subjects treated for TBI using continuous EEG monitoring was therefore prospectively studied. During 7334 hours of EEG recording in 47 patients no electroencephalographic seizures were observed.

Theoretically, and based on animal studies, prostacyclin (PGI_2) can improve the microcirculation of the brain, decreasing the risk for secondary ischaemic brain injury. PGI_2 was introduced to the treatment in a prospective randomised double blinded study (epoprostenol 0,5 ng/kg/min). The effect of PGI1 pkt was analysed using the lactate/pyruvate ratio (L/P) measured by cerebral microdialysis in order to study the energy metabolism in the brain. The outcome was measured as Glasgow Outcome Scale (GOS) at 3 months follow-up. Forty-eight subjects were included. The L/P was pathological high during the first day, thereafter decreasing. There was no significant difference in L/P or outcome between the treated and non-treated group. At 3 months the mortality was 12,5% (95,8% was discharged alive from the ICU), and favourable outcome (GOS 4-5) was 52%.

In the same study the brain injury biomarkers S-100B and NSE were followed twice a day for five days to evaluate brain injury and investigate the possible use of these biomarkers for outcome prediction. Initially the biomarkers were elevated to pathological levels which decreased over time. The biomarkers were significant

elevated in subjects with Glasgow Coma Scale 3 (GCS) and GOS 1 compared with subjects with GCS 4-8 and GOS 2–5, respectively. A correlation to outcome was found but this correlation could not be used to predict clinical outcome.

It is concluded that the ICP measurements are valid and the treatment protocol is a safe and solid protocol, yielding among the best reported results in the world, in regard to favourable outcome as well as in regard to mortality. Epoprostenol in the given dose was not shown to have any effects on the microdialysis parameters nor the clinical outcome. In sTBI L/P and brain injury biomarkers can not be used to predict the final outcome.

List of orginal Papers

I.   Koskinen L-O. D., Olivecrona M.
Clinical Experience with the Intraparenchymal Intracranial Pressure Monitoring
Codman MicroSensor System. Neurosurgery 2005 Apr;56(4):693-8.

II.   Olivecrona M., Rodling-Wahlström M., Naredi S., Koskinen L-O. D.
Effective ICP Reduction by Decompressive Craniectomy in Patients with Severe
Traumatic Brain Injury Treated by an ICP-Targeted Therapy. J Neurotrauma 2007
Jun;24(6):927-35.

III.   Olivecrona M., Zetterlund B., Rodling-Wahlström M., Naredi S, Koskinen L-O. D.
Absence of electroencephalographic seizure activity in patients treated for
head injury with an ICP targeted therapy. Journal of Neurosurgery, DOI:
10.3171.2008.4.17538

IV.   Olivecrona M., Rodling-Wahlström M., Naredi S., Koskinen L-O. D.
Prostacyclin Treatment in Severe Traumatic Brain Injury - A microdialysis and
outcome study. Submitted for publication in Journal of Neurotrauma.

V.   Olivecrona M., Rodling-Wahlström M., Naredi S., Koskinen L-O. D.
S-100B and NSE are Poor Outcome Predictors in Severe Traumatic Brain Injury
treated by an ICP Targeted Therapy. Submitted for publication in Journal of
Neurology, Neurosurgery, and Psychiatry.

Abbreviations

AUC	Area Under the Curve
BBB	Blood Brain Barrier
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
cEEG	Continuous Electroencephalogram
CMS	Codman MicroSensor™
CPP	Cerebral Perfusion Pressure
CSF	Cerebral Spinal Fluid
DAI	Diffuse Axonal Injury
DC	Decompressive Craniectomy
DHE	Dihydroergotamine
EEG	Electroencephalogram
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
HISS	Head Injury Severity Scale
ICP	Intra Cranial Pressure
ICU	Intensive Care Unit
IEU	ICP Express Unit
L/P	Lactate Pyruvate ratio
MAP	Mean Arterial Blood Pressure
NDC	Non (No) Decompressive Craniectomy
NSE	Neuron Specific Enolase
PG-G	Epoprostenol group
PGI_2	Prostacyclin
Plac-G	Placebo group
ROC	Receiver Operated Characteristics
SEM	Standard Error of the Mean
sTBI	Severe Traumatic Brain injury
TBI	Traumatic Brain Injury
TXA_2	Tromboxane A_2

BACKGROUND

Epidemiology

Traumatic brain injury is common. Population based studies from industrialised countries show an incidence of 95 - 546 / 100 000 and year, most rates are in the range of 150 - 300 per 100 000 and year (Bruns and Hauser 2003; Tagliaferri, et al. 2006). A study of TBI seeking attendance at the Emergency Department at Umeå University Hospital showed an incidence of TBI of 354 / 100 000 (Styrke, et al. 2007). In Sweden the annual incidence of hospitalisation for head injury is approximately 250 / 100 000. Head injuries are more common in adolescents and young adults and have a male dominance. The peak incidence in Sweden is in the age group 15 – 25 years of age and in the age above 80 years. A male to female ratio is noted in the range of 2:1 (Andersson, et al. 2003; Kleiven, et al. 2003). The most common reasons for head injuries are falls and motor vehicle accidents. In Sweden almost 75% of the persons hospitalised for head injuries are hospitalised for 2 or less days (Kleiven, et al. 2003; Styrke, et al. 2007).

Severe traumatic brain injury (sTBI) is a small part, approximately 10% of the TBI (Bruns and Hauser 2003; Tagliaferri, et al. 2006). The ratio in Europe between mild: moderate : severe TBI has been given to 22 : 1,5 :1 (Tagliaferri, et al. 2006). In Sweden the incidence of sTBI is reported to be 5 – 8 / 100 000 and year. Of all hospitalised head injuries, the frequency of surgical lesions varies between 0,7 and 4% (Teasdale, et al. 1990). In the Umeå study 98 % of the TBI were mild and moderate (Styrke, et al. 2007).

TBI and sTBI can be fatal diseases. The mortality has been reported to be 28 – 35 / 100 000 (Bruns and Hauser 2003). The mortality in the Umeå material was 0% (Styrke, et al. 2007).

Several attempts have been made to reduce the incidence of sTBI, e.g. improvements of cars, roads, and the compulsory use of seat belts. The number of road accidents and injuries in traffic accidents are over the last years declining in the western world (Sosin, et al. 1995; Andersson, et al. 2003; Kleiven, et al. 2003). Although sTBI is a minority of all head injuries the treatment of sTBI is still an important part in the neurosurgical panorama.

The damage which has occurred at the moment of trauma can not be reversed. The treatment of TBI must thus focus on preventing the occurrence of secondary events, and secondary injuries. This can be achieved in many different ways, e.g. by surgical reduction of mass lesion, treatment of oedema, and reduction of ICP.

In this thesis the treatment of sTBI with an ICP targeted therapy will be in focus. The foundation of the treatment strategy used at the Department of Neurosurgery University Hospital Umeå will be presented. The used treatment guidelines will be discussed in relation to other protocols in use elsewhere. Further, in the light of the five papers on which this thesis is build certain aspects of the treatment and prognosis of sTBI will be examined.

Definition of Severe Traumatic Brain Injury

Different scales have been developed to describe the severity of injury and that of head injury, among others: Abbreviated Injury Score (AIS), Injury Severity Score (ISS), Glasgow Coma Scale (GCS), Head Injury Severity Scale (HISS) and Reaction Level Scale-85 (RLS 85) (Rating 1971; Baker, et al. 1974; Teasdale and Jennett 1974; Starmark, et al. 1988; Stein and Spettell 1995). The most common reasons for the development of these scales have been to have an instrument for the prediction of outcome, as a help to decide about what therapy should be given, or to be able to compare the severity of the injured patients. Through history different definitions of sTBI have been used including duration of loss of consciousness, and the reaction to different stimuli, such as verbal commands or pain stimuli.

The most widely used definition and division of the severity of head injury is based on the level of consciousness as defined by the GCS introduced in 1974 (Teasdale and Jennett 1974). The GCS is an algebraic scale based on motor response, verbal response, and eye opening (**Table 1**). The grading according to GCS should be performed after resuscitation and the best response noted. In modern care for head injury subjects are often intubated and sedated early to minimise the risk for hypoxia and secondary brain injuries. This makes the use of a post-resuscitation GCS very difficult as the subject has to be woken to be adequately scored. Several authors use the GCS at intubation and sedation for the GCS scoring.

The most commonly used definition for the grading of the severity of a head injury is based on the HISS (Stein and Spettell 1995). It defines sTBI as a subject with GCS 8 or worse. The GCS system allows fore the classification of head injuries in different groups, **Table 2**.

The definition of sTBI used in this thesis is a GCS of 8 or worse at sedation and intubation.

Assessment of clinical outcome after severe traumatic brain injury

The most commonly used outcome scale in neurosurgery is the GOS (Jennett and Bond 1975). The scale is outlined in **Table 3**. The scale is based on the overall social

Table 1

Eyes	Opens	Spontaneous	4
		To speech	3
		To pain	2
		No response	1
Best motor response	On verbal command	Obeys	6
	To painful stimulus	Localising	5
		Withdraws (flexion)	4
		Abnormal flexion (posturing)	3
		Extension (posturing)	2
		No response	1
Best verbal response		Oriented conversation	5
		Confused, disoriented	4
		Inappropriate words	3
		Incomprehensible sounds	2
		No response	1
Total			3–15

The Glasgow Coma Scale (Teasdale and Jennett 1974).

Table 2

	Severity Category	GCS Interval	
MINOR	Minimal	15	No loss of consciousness (LOC) or amnesia
	Mild	14–15	GCS 14 or GCS 15 + amnesia or LOC <5 min, or memory disturbance or impaired consciousness
	Moderate	9–13	9–13 or LOC ≥5 min, or focal neurological deficit
SERIOUS			
	Severe	5–8	
	Critical	3–4	

The Head Injury Severity Score (Stein and Spettell 1995).

capability of the patient. It takes in to account neurological as well as mental deficits without listing them. The scale has been proven functional and is recommended world wide for the follow up after head injury (Jennett, et al. 1981; Clifton, et al. 1992; Pettigrew, et al. 2003).

The concept of secondary brain injuries

In the literature of head injury one often encounters the concept of primary and se-condary brain injuries (Miller, et al. 1978; Miller and Becker 1982). Primary injury

Table 3

	Interpretation	Comments
GOS 1	Death	
GOS 2	Persistent vegetative state	Nonsentient survival (Jennett and Plum 1972)
GOS 3	Severe disability	Dependent for daily support 24 hours a day
GOS 4	Moderate disability (independent but disabeld)	Independent, can travel by public transport and work in a sheltered environment. Deficits may be: dysphasia, hemiparesis, personality changes, intellectual and memory changes. The degree of independence is higher than described by "independent for activities of daily life"
GOS 5	Good recovery	Resumption of normal life even with minor neurological or psychological deficits

A summary of the Glasgow Outcome Scale (Jennett and Bond 1975).

is the damage to the nervous system which takes place at the moment of injury. The mechanical forces transmitted to the brain result in deformation of the brain substance and thus till direct injuries to the central nervous system tissue and to the vessels. The result is injuries such as; diffuse axonal injuries (DAI), bleedings, intracerebral haematomas, subdural or extradural haematomas, and contusions. The primary brain injuries are considered to be irreversible.

The secondary injuries are complications to the sustained primary injuries. These injuries are the result of hypoxic and or ischaemic changes to the injured brain which can result in ischaemia, oedema formation, rising of ICP, developing of contusions, and hydrocephalus. The secondary brain damages are potentially reversible if they are observed and adequately treated. The treatment guidelines for sTBI which have been developed are aiming at the treatment or prevention of secondary brain injuries. The strategies are aiming at secure the oxygenation and perfusion to the brain, especially to the injured parts of the brain.

Hypoxia and hypotension, as an indication of secondary brain injury, occurring from the accident through to the resuscitation is shown to be associated with higher mortality and mortality in subjects with sTBI (Chesnut, et al. 1993).

Brain volume regulation

The volume regulation of the brain is more exact than the volume regulation of most other organs in the body. This is necessary as the brain is enclosed in the skull and thus the volume is given. Approximate volumes are: parenchyma 1400ml, blood 100ml, extracellular fluid 125ml, and CSF 125ml.

This regulation is mostly due to a precise control of the fluid exchange over the capillaries in the brain. The capillaries in the brain are different from most other capillaries in the body. They are characterised by the fact that the capillary membrane is only permeable to water and almost impermeable to any other molecules, even to ions like chloride and sodium. The transport mechanisms of most molecules over the brain capillaries are active energy dependent processes through special designated pores and pumps. The tight capillary membrane constitutes what is called the blood-brain-barrier. In brain trauma the BBB can regionally be damaged and thus more permeable allowing for other molecules to freely pass over the BBB.

CSF is produced at a fairly constant rate, so the absorption of CSF is an important part in the volume regulation of the brain. Under physiological conditions the relation of the CSF pressure (ICP), the CSF formation rate (q_f), the CSF outflow resistance (R_o), and the sinus pressure (P_{ss}) can be described by the steady state Davson equation:

$$ICP = (q_f \, x \, R_o) + P_{ss}$$

Regulation of cerebral blood flow and blood volume

There is a tight regulation of the blood flow to the brain. This regulation means that under physiological circumstances the CBF remains fairly constant irrespectively of CPP, within a rather wide range (systolic pressure 60 – 150 mmHg) (Folkow and Neil 1971; Paulson, et al. 1990). The reason for the autoregulation is to secure the brain's need of blood, i.e. oxygen and glucose, if the CPP decreases. With the autoregulation follows that fluctuations in blood pressure are not transmitted to the capillaries and thus the intra capillary hydrostatic pressure remain fairly constant.

The arterial CO_2 level is a very strong modulator of CBF. Hypoventilation causes vasodilatation and hyperventilation causes vasoconstriction (Folkow and Neil 1971; Paulson, et al. 1990). Hyperventilation has for many years been used as a ground pillar for the treatment of increased ICP. Hyperventilation is a way of rapidly decreasing the CBV and so the ICP. The hyperventilation gives rise to a vasoconstriction in the precapillary resistance vessels. Profound hyperventilation can thus give rise to ischaemia due to the vasoconstriction (Cold, et al. 1977; Nwaigwe, et al. 2000). Prolonged hyperventilation seems to have adverse effect on outcome after TBI (Muizelaar, et al. 1991). Many other factors including, neurotransmitters, nitric oxide, peptides, oxygen, and intrinsic and extrinsic nerves influence the CBF (Mraovitch and Sercombe 1996).

Reduction of CBF and CBV can be accomplished by reducing brain metabolism. This can be achieved by infusion of barbiturates (Nordström, et al. 1988). The aim of the barbiturates would be to lower the metabolism and so the need of a normal CBF. Beside the metabolic effect barbiturates have several other effects on the vascular bed of the brain, such as alterations of vascular tone and resistance. Traditionally high dose barbiturates have been used. Eisenberg in his study used a loading dose of 10 mg/kg and then 5 mg/kg every hour for 3 hours and thereafter a maintenance dose of 1mg/kg/h (Eisenberg, et al. 1988). Barbiturates are known to have severe side effects such as hypotension, depression of the immune system and inflammatory response, and cerebral vasoparalysis (Schalen, et al. 1992).

### The Volume – Pressure Curve, The Monro Kellie doctrine

As mentioned above one of the basal physiological principles of neurosurgery and neurotraumatology is the fact that the brain is enclosed within the skull, a non-flexible box. The volumes of the different components within the skull have a tight relationship to each other. This can be depicted in the following equation:

$$ICP \sim V_{intracranial} = V_{brain} + V_{blood} + V_{CSF} + V_x$$

V_x = the volume that disturbs the balance e.g. oedema, contusion, tumour, bleeding. There is a physiological compensation mechanism in this relation striving to keep the ICP as normal as possible. If the V_x increases this will be compensated by an increasing resorbtion of cerebro-spinal fluid (CSF). There is also a possibility to reduce the blood volume within the brain, mainly through reduction on the venous side. This equation can be depicted as the pressure – volume curve (**Figure 1**). As is shown in the figure an initially relatively large increase in the V_x (ΔV_1) results in a fairly small increase in ICP (ΔICP_1) but when the possibility of compensation is fully used, a relatively small increase in V_x (ΔV_2) will cause a large increase in ICP (ΔICP_2). The surgical as well as the non-surgical treatment of a patient with sTBI is aiming at keeping the patient as far to the left on curve as possible by removing surgically or otherwise influence the V_x.

The surgical interventions can be removing of a haematoma, drainage of CSF or even increasing the volume of the skull by performing craniectomy. The removal of haematomas is well documented as the initially perhaps most important step (Mendelow, et al. 1979; Seelig, et al. 1981). The drainage of CSF is well documented as well (Rowbotham 1949). The removal of skull bone, is perhaps the oldest surgical way of treating a trauma patient, and has in recent years seen a renaissance (Schirmer, et al. 2008).

Figure 1
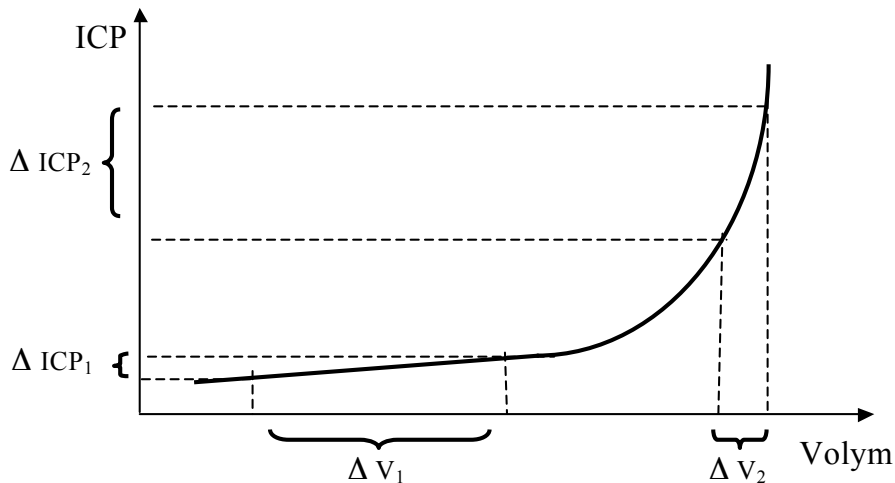
The pressure – volume curve.

Regulation of fluid fluxes over the Blood Brain Barrier

As mentioned earlier the brain is in need of a tight volume control. Therefore fluxes of fluid in and out of the brain have to be more tightly controlled than in other parts of the body. Fluid can not be allowed to move freely over the capillaries in to the brain, causing a swelling and so a volume increase and thereof following increase in ICP. This tight control is achieved by unique quality of the brain capillaries. They are much tighter, not allowing any substance except for water to freely pass over the capillary wall. Even small ions like Na^+ or Cl^- can not freely pass over the BBB.

The flux over a membrane is defined by the hydrostatic pressure on both sides of the membrane, the permeability of the membrane (reflection coefficient) and the osmotic pressure on each side of the membrane. This means that the driving force over the membrane would be the difference between the hydrostatic pressure difference over the membrane and the osmotic pressure difference over the membrane (adjusted for the reflection coefficient). In the brain with an intact BBB the blood pressure has very little influence on the hydrostatic pressure difference. This is firstly due to the autoregulation of the brain circulation which not allows for a transmittance of the blood pressure variations to the cerebral capillaries and secondarily due to the low permeability for solutes over the BBB. There is a high osmotic pressure on both sides of the membrane, as tightness of the membrane makes the solutes on each side of the membrane highly osmotic active. The osmotic pressure is on both sides of the BBB very high, approximately 5700 mosm.

If the BBB is injured it will be more permeable for water and for solutes. The water flux over the membrane will then be more dependent on the difference in hydrostatic capillary pressure and on the difference in osmotic pressure over the injured BBB. In the injured brain it can further be supposed that the autoregulation of the cerebral blood flow can be disturbed, locally, regionally or global. The impaired autoregulation will lead to that changes in the systemic blood pressure will be transferred to the capillary system and thus result in changes in the capillary hydrostatic pressure. The fluxes over the membrane will with a less tight BBB also be more sensitive to changes in osmotic pressure over the BBB (Fenstermacher 1975; Asgeirsson and Grände 1994; Grände, et al. 1997a; Grände, et al. 1997b; Grände, et al. 2002; Nordström, et al. 2003; Schirmer, et al. 2008). This means that an increase in systemic blood pressure and so CPP will lead to an increase in capillary hydrostatic pressure. This increase would result in an increased water flux from the capillary into the extracellular space and so to oedema formation. If the systemic pressure would be decreased and so the CPP the absorption of water into the capillary would increase with a diminished oedema as consequence. The same reasoning applies to changes in the capillary osmotic pressure. An increase of the capillary osmolality would lead to an increased absorption of water in the capillary, and the other way around. The most osmotic active substances in the capillary are Na^+, Cl^-, and albumin.

As a consequence of the importance of the pressure differences over the injured

BBB surgical removal of intracranial expansions such as haematomas or contusion will lead to a decrease in intracranial pressure and so to a decrease in tissue pressure in the brain. A decrease in tissue pressure in the brain can lead to an increased flux of water across the injured BBB as the pressure difference over the BBB is altered (a relative increase in the capillary hydrostatic pressure over the BBB). The effect can be seen as an increase of oedema formation and thus an increase in ICP, a phenomenon not seldom seen after a surgical intervention. The oedema formation will continue until a new equilibrium of pressures over the BBB is formed.

This would underline the importance of the combination of surgical and non-surgical i.e. intensive care treatment for patients with sTBI. The intensive care treatment has to be carried on before, during, and after surgical interventions.

In 1994 the 2 pore theory was introduced by Rippe and Haraldsson (Rippe and Haraldsson 1994). The theory means in short that there is a passive transport of fluid across the capillary membrane. This passive transport goes through small and large pores in the capillary. Proteins also pass the membrane passively but can only do this through the less common larger pores mainly localised on the venous side of the capillaries. This theory would indicate that the transcapillary hydrostatic pressure is of importance not only for the fluid exchanges over the capillaries, but also for the protein exchange. The theory also underlines the importance of the colloid osmotic pressure for the prevention of extravasation of fluid.

Treatment of Severe Traumatic Brain Injury

The treatment of sTBI has long interested man. In archaeological findings skulls with signs of trephination have been found. Hippocrates and Galen described indications for trephination due to skull fractures (Kshettry, et al. 2007).

With the development of modern medicine came also the development of modern neurosurgery and modern treatments for sTBI. Still in the middle of the 20th century the main treatment for patients with brain trauma was; bed rest (no head elevation), warm blankets, observation (pupils, blood pressure, respiration), and dehydration (50 ml of glucose 50%). In very few cases mostly in suspected depressed fractures, which could be diagnosed by x-ray and suspected epidural haematomas, surgery was recommended (Nielsen 1941). As an additional monitoring and therapy, repeated lumbar puncture, with pressure measurement and withdrawal of CSF to lower the pressure was advocated (Rowbotham 1949).

During the period 1960 – 1990 there was an increasing aggressiveness in the treatment of sTBI. The introduction of modern intensive care, ventilation and sedation of patients influenced the treatment. Patients were treated with hyperventilation, iterated doses of mannitol, and head elevation. The improvement of neuroradiology, foremost the introduction of the CT-scan, allowed for better diagnoses and more aggressive neurosurgery as it allowed for direct visualisation of intracranial injuries, such as fractures, epidural and subdural heamatomas, and contusions (Le-

vander, et al. 1975). In the 1980-ies mortality in sTBI was reported in the ranges of 35 – 50% (Langfitt and Gennarelli 1982; Nordström, et al. 1989).

The poor results of the treatment for sTBI led in Lund, Sweden, to the development of treatment guidelines based on the physiological principles for the volume regulation of the brain. The group in Lund focused on the normalisation of the ICP. This treatment concept is known as the "Lund concept" or an "ICP targeted therapy" (Asgeirsson, et al. 1994). Approximately at the same time in the United States Rosner and colleagues proposed a treatment for TBI injuries based on the principle of preserving the circulation of the brain by securing the level of CPP. This regimen has been shortly called a "CPP targeted therapy" (Rosner and Daughton 1990). Also around the same time, in the United States, the Brain Trauma Foundation in co-operation with several other organisations among others the American Association of Neurological Surgeons, and Congress of Neurological Surgeons, published "Guidelines for the Management of Severe Traumatic Brain Injury", shortly "the US-guidelines" (Bullock 1996). These guidelines are based on an inventory of the scientific foundation for the treatment of sTBI. In latter half of the 1990-ies the European Brain Injury Consortium published their guidelines for the treatment of sTBI (Maas, et al. 1997). A comparison between different treatment guidelines is done in **Table 4**.

ICP-targeted therapy, the Lund Concept

In 1994 Asgeirsson, Grände and Nordström published a paper with the title "A new therapy of post-trauma brain oedema based on haemodynamic principles for brain volume regulation" (Asgeirsson, et al. 1994). In this paper they reported on the treatment of 11 severely head injured patients with raised intracranial pressure and impaired reactivity to hyperventilation. They were treated according to a new protocol based on the above mentioned principles for volume regulation of the brain. Out of these 11 patients 9 survived with favourable outcome GOS 4 – 5 and two patients died. Shortly thereafter we in Umeå started to treat the patient according to this concept.

The Umeå treatment protocol, based on the "Lund concept"

The treatment protocol is based on the publications from Lund (Asgeirsson, et al. 1994; Grände, et al. 1997a; Grände, et al. 1997b; Grände, et al. 2002). The aim of the guidelines is to bring the ICP under control. The guidelines rest beside an aggressive neurosurgical approach on four corner stones: at a reduction of the stress response and energy metabolism, control of the capillary hydrostatic pressure, further control of the colloid osmotic pressure and fluid balance, and lastly a reduction of the cerebral blood volume. The basis for this is the physiological principles of fluid fluxes over the BBB that has been outlined above.

Table 4

	US Guidelines 1995	US Guidelines 2007	Umeå Guidelines	Rosner	EBIC
Blood pressure	Hypotension (SBP< 90 mmHg) must be scrupulously avoided *Guideline* MAP > 90 mmHg *Option*	Should be monitored hypotension avoided (SBP < 90 mmHg) *Level II*	SBP > 90 mmHg	SBP > 90 mmHg	SBP > 90 mmHg
Oxygenation	Apnoea or cyanosis in the field or P_aO_2 < 8 kPa must be scrupulously avoided *Guideline*	Should be monitored, hypoxia avoided (P_aO_2 < 8 kPa or S_aO_2 < 90%) *Level II*	P_aO_2 >12 kPa	S_aO_2 > 90% P_aCO_2 > 4,6 kPa	S_aO_2 > 95% P_aO_2 > 13 kPa P_aCO_2 4–4,5 kPa
Analgesics, and Sedatives	N/A	Mentioned	All pts sedated using midazolam and fentanyl to comfortable level (coughing)		
Muscle Relaxation	N/A	N/A	Not used	Pancuronium bromide, to maintain slow, even ventilation and avoid problems with ventilator management	

	US Guidelines 1995	US Guidelines 2007	Umeå Guidelines	Rosner	EBIC
Indication for Intracranial Pressure Monotoring	In pts with sTBI and abnormal CT scan *Guideline* Is appropriate in pts with sTBI and normal CT scan if two or more of the following are noted at admission; Age > 40 years, uni- or bilateral motor posturing, SBP < 90 mmHg *Guideline*	ICP measured in all salvageable pts with sTBI and abnormal CTscan of the brain *Level II* ICP monioring in pts with sTBI and normal CT if two or more of the following: age > 40 years, bilateral motor posturing, or SBP < 90 mmHg *Level II*	All pts with sTBI	All pts with sTBI	"...considers ICP measurement desirable..."
Intracranial Pressure Monitoring Technology	1. Intraventricular devices 2. Parenchymal catheter tip pressure devices 3. Subdural devices 4. Subarachnoidal fluid-coupled device 5. Epidural devices	Ventricular catheter Fiberoptic or Micro strain gauge catheters	Micro strain gauge catheter (Ventricular catheter)	Ventriculostomy	N/A
Intracranial Pressure Threshold	20–25 mmHg *Guideline*	Treatment initiated at ICP > 20 mmHg *Level II*	ICP > 20 mmHg	N/A	20–25 mmHg

	US Guidelines 1995	US Guidelines 2007	Umeå Guidelines	Rosner	EBIC
Cerebral Perfusion Pressure Threshold	CPP > 70 mmHg *Option*	Aggressive attempts to maintain CPP > 70 mmHg with fluids, and pressors should be avoided *Level II* CPP < 50 mmHg avoided *Level III*	CPP > 50 mmHg	CPP > 70 mmHg	CPP 60–70 mmHg
Barbiturates	High-dose barbiturate may be considered *Guideline*	Prophylactic barbiturates to induce burst suppression on EEG not recommended *Level II* High dose barbiturate recommended to control high ICP *Level II*	Low dose thiopental under cEEG, continuous delta	Not used	"…if ICP is refractory to other treatment modalities."
Hyperosmolar therapy	Mannitol is effective for control of raised ICP. Dose 0,25–1 g/kg *Guideline*	Mannitol effective to control ICP (0,25–1 g/kg) *Level III*	Mannitol rescue drug	Mannitol if CPP < 70 mmHg secondary to rise in ICP	Mannitol, S-Osm < 315 mOsm

	US Guidelines 1995	US Guidelines 2007	Umeå Guidelines	Rosner	EBIC
Hyperventilation	In absence of increased ICP chronic prolonged hyperventilation ($P_aO_2 < 3,3$ kPa) should be avoided *Standard* Prophylactic hyperventilation ($P_aO_2 \leq 4,6$ kPa) during the first 24 h after sTBI should be avoided *Guideline*	Prophylactic hyperventilation not recommended *Level II* Hyperventilation as a temporising measure for reduction of ICP *Level III* Hyperventilation during the first 24 h should be avoided *Level III*	Normoventilation (P_aCO_2 4,5-5,5 kPa) Hyperventilation as rescue measure	Continuous hyperventilation not used	Allowed ($P_aCO_2 <$ 30 mmHg)
CSF drainage	N/A	N/A	Used, to cut peaks, not continuous open	As needed, to control CPP	Used
Fluid balance / Fluids	N/A	N/A	Normovolemia Hb > 110 g/l S-Alb > 40 g/l S-Na$^+$ 135-150 mmol/l	Normovolemia to moderate hypervolemia (CPW 12-15 mmHg, CVP 8-10 mmHg) Hematocrit 30-35% Normovolemia	Intravenous fluids to maintain normal biochemistry and normal blood volume
Vasopressors / Inotropes	N/A	Pressors should be avoided *Level II*	To be avoided, not used	Used Phenylephrine	May be used

	US Guidelines 1995	US Guidelines 2007	Umeå Guidelines	Rosner	EBIC
Deep Vein Thrombosis Prophylaxis	N/A	Compression stockings. Low molecular weight heparin *Level III*	Compression stockings. Low molecular weight heparin	N/A	N/A
Nutrition	Replace 140% of resting metabolism expenditure in non-paralysed pts, 100% in paralysed. Enteral or parenteral, at least 15% as protein *Guidelines* Preferable is the use of jejunal feeding by gastrojejunostomi *Option*	Full caloric replacement on day 7 *Level II*	Early (2nd day) enteral feeding (20 kcal/kg/d)	No alimentation until CPP and ICP was controlled for 24 h by CSF drainage only	Early enteral feeding
Blood grucose	N/A	N/A	3–8 mmol/l	N/A	Should be controlled
Antiseizure Prophylaxis	Is not recommended *Standard*	Prophylatic phenytoin or valproate not recommended *Level II*	No AEDs	N/A	"Prophylactic anticonvulsant therapy is rarely used in Europe but in American neurosurgical centres Phenytoin is routinely administered..."
Prophylactic Hypothermia	N/A	No significant decrease in mortality *Level II*	Not used, normothermia	Not used, normothermia	N/A

| | US Guidelines | US Guidelines | Umeå Guidelines | Rosner | EBIC |
	1995	2007			
Steroids	Is not recommended *Standard*	Not recommended *Level I*	Not used	N/A	No indication

AEDs = antiepileptic drugs, cEEG = continuous EEG monitoring, CPP = Cerebral perfusion pressure, CPW = cardio pulmonary wedge pressure, CVP central venous pressure, EEG = Electroencepholagraphy, h = hours, ICP = Intracranial pressure, N/A = Not available, pts = patients, SBP = systolic blood pressure, sTBI = severe traumatic brain injury (GCS 3 -8),

Comparison between "US-Guidelines" (Bullock 1996; Guidelines 2007), Umeå treatment guidelines after the "Lund concept", Rosner's treatment protocol (Rosner and Daughton 1990; Rosner, et al. 1995), and the European Brain Injury Consortium's (EBIC) Guidelines (Maas, et al. 1997).

In the following a step wise short summary of the treatment protocol is given. **Figure 2** summarises the treatment.

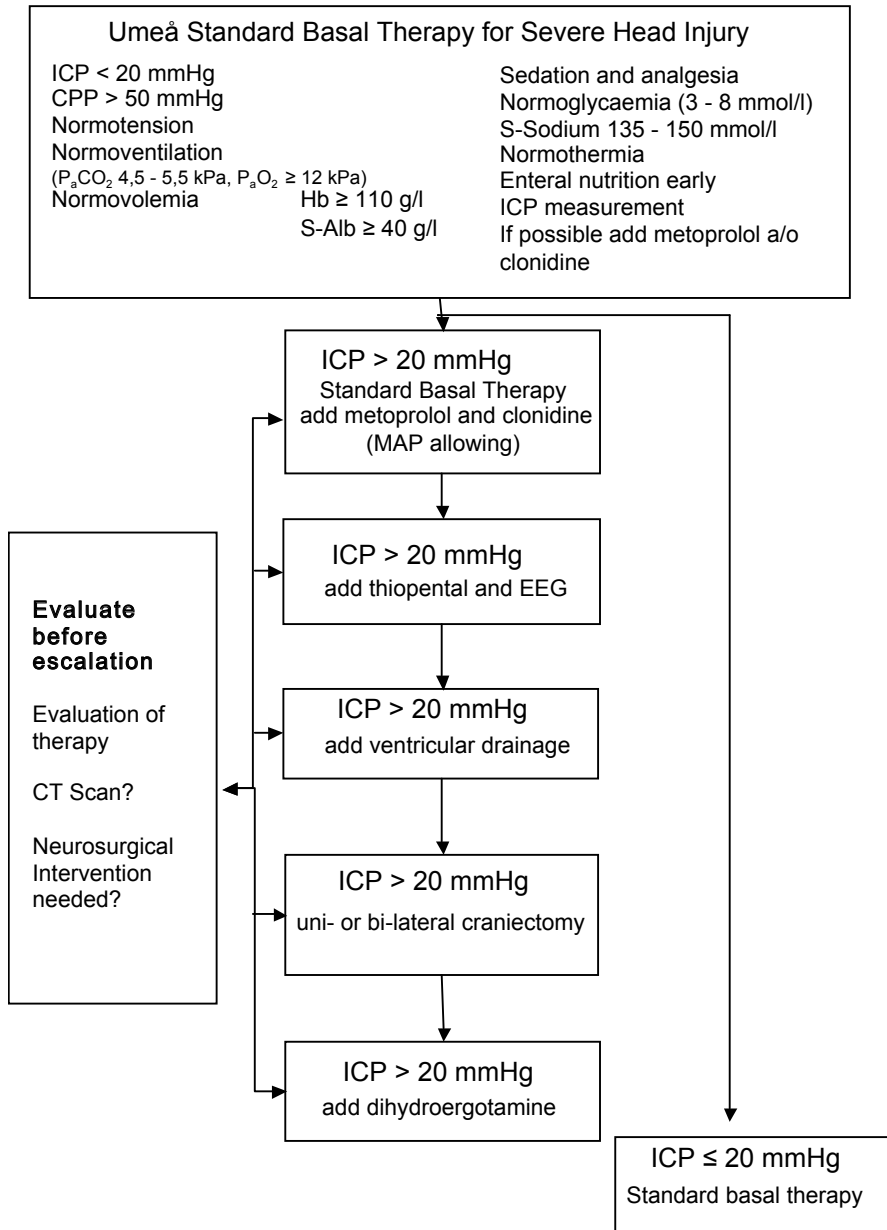### *Treatment at the primary receiving hospital and or site of accident*

Patients with a head trauma and who are unconscious (GCS ≤8) at the site of accident and or on arrival to the primary receiving hospital should be considered being patients with sTBI. Early sedation and intubation is recommended. Patients, who initially are conscious, but become unconscious, should be regarded as sTBI patients. The general management of the patients should follow the intentions of the guidelines of the ATLS® concept (Advanced Trauma Life Support®, American College of Surgeons). A trauma CT scan (Leidner and Beckman 2001) including the brain should be performed and contact with a neurosurgeon taken. If there is need for damage control surgery this should be done at the local hospital, to allow the patient to be transferable. The patient should be normo-ventilated and sedated. Even if the CT scan does not show any intra-cranial pathology contact with a neurosurgeon should be taken. Most of these patients should be transferred to a facility with neurosurgical service. In 2005 an article in the Lancet found that the mortality in patients with head injury was 26% higher if they were treated in a hospital without neurosurgical service (Patel, et al. 2005).

Basal treatment

On arrival in the ICU of the neurosurgery the patient is examined. The guidelines do not recommend awakening test. The patients are kept sedated and ventilated. If the CT scan of the brain from the primary receiving hospital indicates the need for a surgical procedure the patient is taken immediately to surgery, if it is deemed necessary a CT is performed on the way to surgery. The indication for surgery is removal of intracranial expansions such as epidural and subdural haematomas and contusions. Even the removal of relatively small contusions may be considered, especially if the ICP is elevated. After the operation the patient with an ICP monitor is transferred back to the ICU.

If no indication for immediate surgery is indicated on the primary CT scan of the brain an ICP measuring device, most common a Codman MicroSensor™ (CMS) (Johnson & Johnson Professional Inc., Raynahm, MA, USA), should be placed as soon as possible. If then indicated a new CT scan will be performed. The patient will be treated in the ICU.

All patients are sedated, ventilated and given analgesia, using midazolam for sedation and fentalyl for analgesia. The patient should be sedated to a comfortable level, allowing them to cough. The sedation is lowering the stress level and also the brain metabolism, and thus the brain's demands. Patients are treated in the supine position initially without head elevation. The patient is normo-ventilated (P_aO_2 4,5 − 5,5 kPa) with a P_aO_2 >12 kPa. One of the main corner stones of the treatment guidelines is to aggressively maintain normovolemia. This is achieved by infusions of packed red blood cells (Hb > 110 g/l), and albumin (S-alb >40 g/l), which also helps to establish a normal

Figure 2

Umeå Standard Basal Therapy for Severe Head Injury

ICP < 20 mmHg
CPP > 50 mmHg
Normotension
Normoventilation
(P_aCO_2 4,5 - 5,5 kPa, P_aO_2 ≥ 12 kPa)
Normovolemia   Hb ≥ 110 g/l
                      S-Alb ≥ 40 g/l

Sedation and analgesia
Normoglycaemia (3 - 8 mmol/l)
S-Sodium 135 - 150 mmol/l
Normothermia
Enteral nutrition early
ICP measurement
If possible add metoprolol a/o clonidine

ICP > 20 mmHg
Standard Basal Therapy
add metoprolol and clonidine
(MAP allowing)

ICP > 20 mmHg
add thiopental and EEG

Evaluate before escalation

Evaluation of therapy

CT Scan?

Neurosurgical Intervention needed?

ICP > 20 mmHg
add ventricular drainage

ICP > 20 mmHg
uni- or bi-lateral craniectomy

ICP > 20 mmHg
add dihydroergotamine

ICP ≤ 20 mmHg
Standard basal therapy

The Umeå treatment protocol based on the "Lund concept".

colloid osmotic pressure. A normal serum sodium is maintained (135 -150 mmol/l) and crystalloid fluids and furosemide is given to maintain a neutral to slightly negative fluid balance. The blood pressure is kept within normal limits. The CPP is not allowed below the level of 50 mmHg. Blood glucose is kept within normal values (3 – 8 mmol/l) if necessary using insulin and the patients are kept normothermic. Enteral feeding is started (20 kcal/kg/d) early. It is further important to try to avoid bowel paralysis. If the patient is circulatory stable and MAP allows metoprolol (β_1-antagonist) and clonidine (α_2-agonist) can be introduced in the basal therapy, with the aim of reducing the sympathetically mediated stress in the patient, and keeping the blood pressure within normal limits. The choice of these drugs is depending on the fact that they have little or no effect on the cerebral circulation (Asgeirsson, et al. 1995a). Further more β_1-blockade is suggested to be protective after head injury reducing sympathetic nervous system effects on the heart and the lungs (Clifton, et al. 1983; Colgan, et al. 1983; Cruickshank, et al. 1987; Kaufman, et al. 1993). In the last years their have been indications of the beneficial effect of ß-blockade in head injury, improving outcome (Cotton, et al. 2007; Riordan, et al. 2007; Inaba, et al. 2008) Clonidine is reducing the stress response through reduction of sympathetic and catecholamine outflow (Payen, et al. 1990).

If ICP > 20 mmHg

If the ICP in spite of basal treatment climbs above 20 mmHg, a new CT scan of the brain is performed to rule out the need for any surgical intervention. If not started before, infusion of metoprolol and clonidine is started if the patient is circulatory stable. The indication for these drugs is in this situation, besides the stress reducing effect, to reduce the MAP to a normal level according to age and so to reduce the CPP in order to achieve a reduction of the hydrostatic transcapillary pressure and hereby to reduce the leakage over an injured BBB. A decrease in CPP below 50 mmHg in adults is not allowed. This level is regarded as a safety level and has been shown not to provoke ischaemia in the brain (Nordström, et al. 2003).

If ICP > 20 mmHg + basal treatment + metoprolol and clonidine

CT scan of the brain is performed to rule out any need for neurosurgical intervention. Following a re-evaluation of the therapy given, a low dose continuous thiopental infusion without preceding bolus injection is started, in a dosage of 0,5 – 2 mg/kg/h. Thiopental is shown to reduce cerebral metabolism and so reducing CBF and in this way also achieving a reduction in ICP. To monitor the depth of sedation cEEG monitoring is used. The aim is a continuous delta pattern on the EEG.

If ICP > 20 mmHg + basal treatment + metoprolol and clonidine + thiopental

The need for a CT scan of the brain is considered in order to rule out any neurosurgical approachable cause of the ICP elevation. The treatment given so far is evaluated. If there is no indication for a neurosurgical intervention and the patient is optimally treated, a ventricular drainage is inserted. The ventricular drainage is used for intermittent drainage of CSF in small amounts in order to reduce the ICP and to cut peak values of ICP. The drain is not kept open as this would increase the risk for ventricular collapse and the reduction of the tissue pressure, increasing the risk for increased hydrostatical leakage over the BBB and so an increased formation of extracellular oedema.

If ICP > 20 mmHg + basal treatment + metoprolol and clonidine
+ thiopental + ventricular drainage

As before the other steps of escalation, a CT of the brain should be considered and the so far given therapy evaluated. If no surgically approachable reason for the ICP elevation is detected a uni- or bi-lateral hemicraniectomy is performed. The aim with the craniectomy is to expand the volume of the skull. The craniectomy is performed on the radiological most expansive side, and if the expansion is symmetrical bilateral craniectomy is performed. The aim is to perform a temporo - fronto - parieto - occipital craniectomy not smaller than 12 cm in the anterior posterior direction and 8 cm in the cranio caudal direction. To achieve maximum volume a large duraplasty is made using dura substitute, not smaller than 10x4 cm.

If ICP > 20 mmHg + basal treatment + metoprolol and clonidine + thiopental
+ ventricular drainage + hemicraniectomy

If no surgically approachable explanation for the persistent increase of ICP in spite of the above undertaken measures DHE can be considered an option for bringing the ICP under control. The ICP reducing effect of DHE is mainly due to its capability to reducing the blood volume of the brain by constriction of the venous capacitance vessels. DHE also gives rise to a precapillary vasoconstriction and so to a reduction of the capillary hydrostatic pressure (Mellander and Nordenfelt 1970; Grände 1989; Asgeirsson, et al. 1995b). Over the years the use of DHE in the therapy for sTBI has become more and more rare.

Outcome in patients treated for severe traumatic brain injury using a treatment protocol based on the "Lund concept"

In the literature there are four publications on the outcome in adult patients treated for sTBI using a ICP targeted protocol based on the "Lund concept". These together with data from Paper IV are shown in **Figure 3** (Eker, et al. 1998; Naredi, et al. 1998; Naredi, et al. 2001; Olivecrona, et al. 2007). Results in the same range have

been reported from Münster, Germany (Scherer, et al. 2008). Data on paediatric sTBI treated by an ICP guided protocol based on the "Lund principles" was published 2005 (Wahlström, et al. 2005). In this paper the follow up on 40 paediatric patients was presented showing a mortality of 7,5%, unfavourable and favourable outcome in 12,5% and 80%, respectively.

Figure 3
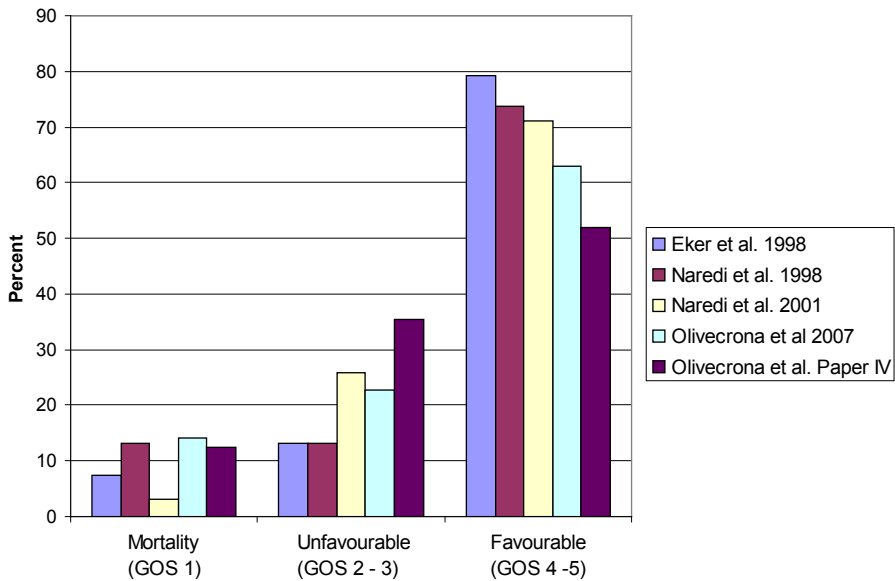
Outcome in adult patients treated for severe traumatic brain injury with a protocol based on the "Lund concept".

Cerebral Perfusion Pressure targeted therapy

In the 1980-ies the suggestion was made that a high CPP would be beneficial in sTBI patients (Gray and Rosner 1987; El-Adawy 1989; McGraw 1989). Rosner and Daughton suggested in a paper 1990 that the CPP should be maintained above 70 mmHg (Rosner and Daughton 1990). The concept of the therapy is based on the autoregulatory effects of the CPP on the cerebral vasculature. The cerebral trauma shifts the autoregulatory curve to the right so the brain should need higher CPP levels to maintain the CBF. This shift of the autoregulation curve to the right is meant to be due to an increase of the cerebral vascular resistance. Decrease in CPP is preceding Lundberg A or B waves, which are interpreted as signs of ischaemia. If CPP would be stabilised at a level above the limit of creating A and B waves the brain would be secure of ischaemia. They reported on 34 patients with TBI (admission GCS 3 – 13) treated according to this principle. The treatment protocol included intubation, ICP monitoring, precise

fluid therapy, controlled electrolyte balance, systemic pressure drugs to maintain CPP, mannitol when the CPP declined, normoventilation and infusion of packed red blood cells to maintain a haematocrit of 30 – 35%. In this paper the mortality was 21% and favourable outcome (GOS 4-5) 68% (Rosner and Daughton 1990).

In 1995 Rosner and co-workers reported a series of patients with sTBI (admission and postresuscitation GCS ≤ 7) treated according to the guidelines outlined above (Rosner, et al. 1995). In this study 158 patients with an initial median GCS of 5 and mean age of 27,9 years were included. A mortality of 29% and a favourable outcome (GOS 4-5) in 59% was reported. **Table 4** compares this treatment strategy with other treatment guidelines.

A prospective trial comparing a CPP targeted protocol (CPP > 70 mmHg) with a more conventional ICP targeted protocol (CPP > 50 mmHg) not based on the "Lund principles" showed no difference in outcome between the groups but showed a five-fold higher frequency of acute respiratory distress syndrome in the patients treated in the CPP targeted protocol (Robertson, et al. 1999; Robertson 2001).

Guidelines for the Management of Severe Traumatic Brain Injury, "US guidelines"

In 1996 the Brain Trauma Foundation in the Journal of Neurotrauma published guidelines for management of traumatic brain injuries (Bullock 1996). The aim was to scrutinise the literature and establish the scientific foundation for the treatment of sTBI. The guidelines were divided in chapters on different parts of the treatment. Three levels of recommendations were used: *standards:* "accepted principles of patient management and reflect a high degree of clinical certainty", *guidelines:* "a particular strategy or range of management that reflect a moderate clinical certainty" and *options:* "the remaining strategies ...for which there is unclear clinical certainty". The guidelines have since 1996 been revised two times (Bullock 2000; Guidelines 2007). The last revision was published in Journal of Neurotrauma in the spring 2007 (Guidelines 2007). In this the 3rd edition of the guidelines the levels of recommendations were changed from the above mentioned to Level I, Level II, and Level III, respectively. The terminology is based on the evidence classes I – III. This means that recommendations *Level I* are based on the strongest evidence and reflects a high degree of certainty. In the *Level II* the degree of clinical certainty is moderate and in *Level III* the level of certainty has not been established. In **Table 4** a comparison between the "US-guidelines" from 1995 and 2007 are compared with the Umeå treatment guidelines. As is shown in the **Table 4**, the two treatment strategies have over the years come closer to each other.

European Guidelines for treatment of severe head injury

In 1997 The European Brain Injury Consortium (EBIC) published guidelines for the treatment of sTBi in adults (Maas, et al. 1997). These guidelines were based on

consensus and expert opinion. In **Table 4** the guidelines are summarised and compared with other published and used guidelines.

Intracranial pressure and pressure measurement

The importance of the intracranial pressure and the implications of a rised ICP have been recognised for a long time (Kocher 1901; Cushing 1905). The lumbar puncture has been a method used for measuring of the intracranial pressure (intralumbar pressure). Lundberg in his thesis 1960 described a method of continuous registration of the ICP (Lundberg 1960). He describes the ICP-waves and their interpretation. The work by Lundberg established continuous ICP monitoring as a clinical tool for monitoring patients in risk of an elevated ICP. A way of measuring the ICP has since the 1940-ies been the use of a ventricular catheter or needle and so measuring the pressure by using the fluid pillar (Ingraham 1941). Later other techniques have been used, based on the same principle but registering from the epidural or subdural space. The use of a ventriculostomy and a fluid pillar system is still recognised as the golden standard for the measurement of ICP. All new introduced techniques are compared to the golden standard (ventriculostomy) for the establishing of accuracy and reliability. The ventricular catheter technique is probably the cheapest method of measuring the ICP but is connected with complications fore most infections but also haemorrhages (Sundbärg, et al. 1988; Paramore and Turner 1994). There are also technical malfunctions with the ventriculostomy such as obstruction and misplacement.

Alternative techniques for the measurement of ICP have been introduced, such as intraparenchymal techniques based on catheter tip strain gauge or fiberoptic technology. The presumed advantages with these catheters are a lower frequency of complications such as haemorrhages or infections and an easier surgical procedure at implantation. Doubts have been risen as most of these catheters can not be calibrated after insertion, and thus the drift of the device not be checked until the device is explanted.

The routine use of ICP measurement in all patients treated for sTBI is even today not self-evident (Murray, et al. 1999; Guidelines 2007; Smith 2008).

Decompressive Craniectomy

To remove parts of the vault of the skull is an old technique to achieve room for the expansion of the brain. In modern times the technique was described in the early 1900 for tumour patients (Kocher 1901; Cushing 1905). Already Kocher and Cushing understood the importance of not only opening the skull bone but also opening the underlying dura to allow for maximal swelling of the brain. During the last 10 - 20 years there has been an increasing interest in the procedure. Several papers have been published on DC in sTBI (Gaab, et al. 1990; Kunze, et al. 1998; Hejazi, et al. 2002; Kontopoulos, et al. 2002; Albanese, et al. 2003; Hutchinson, et al. 2006; Howard, et al. 2008; Timofeev, et al. 2008). The procedure of DC has also found its

place in the treatment of malignant media infarction (Kondziolka and Fazl 1988; Rieke, et al. 1995; Schwab, et al. 1995; Schwab, et al. 1998; Malm, et al. 2006).

The common problem in the literature is that most of the papers are not stringent in their reports of the materials, methods, or results. For example there is heterogeneity in the material, insufficient statements of treatment protocols used, or size and technique of craniectomy. The same inconsistency is found in the literature in regard to the effect on ICP or outcome.

An important factor when giving the indication for hemicraniectomy is the understanding of that the procedure is a major intervention in the physiology of the brain. Moreover the decision to perform a hemicraniectomy is at same time a decision to operate the patient once again. The physiological effects of the hemicraniectomy influence the oedema formation in the injured brain, has effects on the CBF, and on the rehabilitation of the patient (Fodstad, et al. 1979; Fodstad, et al. 1984; Winkler, et al. 2000; Akins and Guppy 2008). If a DC is performed the skull bone should be replaced as soon as possible in order to facilitate the rehabilitation.

EEG, subclinical seizures and secondary brain injury

There has been a rising interest in cEEG monitoring during intensive care for neurological disorders including head trauma. There are several reasons for this e.g. EEG is tightly linked to cerebral metabolism, EEG is sensitive to ischaemia, and EEG can detect subclinical seizures (Ingvar, et al. 1976; Nuwer and Jordan 2000). Subclinical epileptic seizures are increasing the metabolic demand of the brain, and thus due to ischaemia can cause secondary injuries to the brain. Subclinical seizures are claimed to affect the outcome in patients under neurointensive care (Synek 1988; Young, et al. 1996). Vespa and co-workers reported of increase in extracellular glycerol measured by cerebral microdialysis as a sign of cellular death (Vespa, et al. 2002). These findings supported earlier findings from the same group where increase in extracellular glutamate was found in cerebral microdialysis from patients with subclinical seizures (Vespa, et al. 1998). This would indicate that the detection and treatment of subclinical seizures are important for the prognosis of the patient with sTBI.

Prostacyclin

Prostacyclin is a potent vasodilator and an inhibitor of leukocyte activation and adhesion as well as an inhibitor of platelet aggregation. PGI_2 is synthesised in the vascular endothelium (Moncada, et al. 1976; Moncada and Amezcua 1979; Moncada and Vane 1979). In the healthy subject there is a balance between PGI_2 and thromboxane A_2 (TXA_2). In trauma this equilibrium is shifted towards TXA_2 (Gryglewski, et al. 1978; Moncada and Amezcua 1979; Vane and Corin 2003). With the relative reduction of PGI_2 concentrations follows the risk of impaired microcirculation due

to vasoconstriction, augmented leukocyte adhesion and platelet aggregation. In experimental situations of traumatic brain injury it has been shown that PGI_2 can have valuable effects on the microcirculation but also on the permeability of the capillary system (Möller and Gründe 1997; Bentzer, et al. 1999; Möller and Gründe 1999b; Möller and Gründe 1999a; Bentzer, et al. 2001a; Bentzer, et al. 2001b). In 2000 Gründe and co-workers published results in 5 patients with sTBI in whom epoprostenol, a commercially available PGI_2, was said to have some beneficial effects on the brain energy metabolism as measured by microdialysis (Gründe, et al. 2000). If so, PGI_2 could be an option in the treatment of sTBI.

Microdialysis

The technique of cerebral microdialysis was introduced in the 1970ies (Delgado, et al. 1972; Ungerstedt and Pycock 1974). Among the first publications of the use of microdialysis in the human brain were Meyerson et al. 1990 and Hillered et al. the same year (Hillered, et al. 1990; Meyerson, et al. 1990).

The microdialysis is based on the passive diffusion of substances over a semipermeable membrane. Substances are diffusing from higher to lower concentration. The microdialysis catheter is a double lumen catheter, were the dialysate is pumped in the inner catheter and at the tip out in the space between the inner catheter and the outer semi-permeable membrane and allowing for passive diffusion from the outside towards the inside. The composition of the dialysate is important for the concentration gradient over the membrane (**Figure 4**). The diffusion over the membrane is dependent on the following characteristics (Benveniste and Huttemeier 1990; Ungerstedt 1991; Hutchinson, et al. 2000):

Figure 4
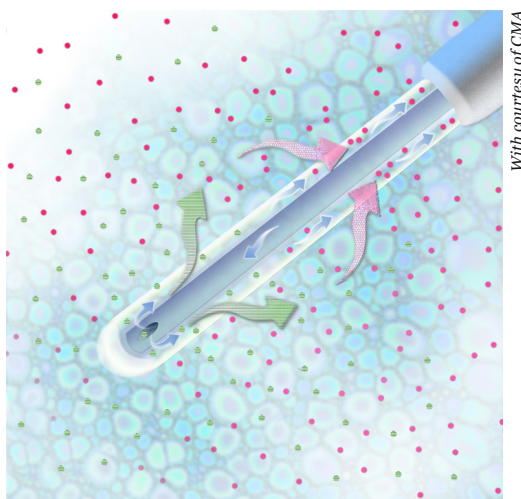
With courtesy of CMA

The tip of the micodialysis catheter with the microdialysis membrane.

1. the flow rate of the perfusion fluid (the lower the perfusion rate the higher the recovery)

2. the length of the membrane (the longer the membrane the higher the recovery)

3. the properties of the membrane (the permeability "the holes" in the membrane, defining the maximum seize of the substance that can penetrate the membrane (kDa))

4. the diffusion coefficient of the substance (higher molecular weight corresponds lower diffusion coefficient).

Cerebral microdialysis has foremost been used to study the cerebral metabolism by analysing the cerebral extracellular content of glucose, pyruvate, lactate, and glutamate.

Glucose

Glucose is the main energy substrate for the brain. There is a fast transport of glucose between the capillaries, the extracellular space, and the intracellular space. The intracellular concentration of glucose is decreasing rapidly if the supply is diminished, which would correspond to ischaemia. With this rapid decrease in intracellular glucose concentration follows a rapid decline in extracellular glucose concentration. Thus would an ischaemia of the brain result in decreased concentration of glucose in the microdialysis. The normal value of the cerebral extracellular glucose concentration measured by microdialysis using a catheter with 20 kDa permeability and a flow rate of 0,3 μl/min is supposed to be 1,7 ± 0,9 mmol/l (Reinstrup, et al. 2000). For practical reason 2,0 mmol/l is considered to be the normal value.

Lactate Pyruvate Ratio

Lactate and pyruvate are parts of the glycolytic chain. The lactate pyruvate ratio (the quota between the two) is an accepted marker of the redox state of the tissue (Granholm and Siesjö 1969; Siesjö 1978). An increased L/P would indicate ischaemia or brain metabolic disturbances (Persson and Hillered 1992; Vespa, et al. 2005). Simultaneous and parallel increase in lactate and pyruvate concentration keeping the L/P unchanged may indicate an increased glycolytic rate. The upper normal limit for the L/P has been suggested to be 20 (Reinstrup, et al. 2000).

Biomarkers for brain injury

During the last decades several biomarkers have found their use in clinical medicine e.g. troponine for myocardial infarction, and prostate specific antigen for prostate carcinoma. There have been several attempts to find biomarkers for brain injury. In the 1970-ies there was an interest in creatine kinase and its subunits (Rabow and Hedman 1979; Rabow and Hedman 1985). During the last decades one have tried to find biochemical markers that would allow for prognostication of severeness of

brain injury, to allow for the decision whether or not to hospitalise a patient after head injury or to prognosticate and so be of help in the decision to treat or not. The most studied markers for this purpose have been S-100B and NSE.

S-100 B

S-100 is a protein family of calcium binding proteins. Intracellular S-100B inhibits the microtubule assembly. Extracellular S-100B can be neurotrophic, involved in neuronal development and brain cell repair. This effect is concentration dependent and is found in the nano molar levels. In micro molar concentrations S-100B seems to be stimulating apoptosis in vitro. An over expression of S-100B have been found to be linked to neurodegeneration. Such over expression has been found in Down's syndrome Alzheimer's disease and epilepsy (Sheng, et al. 1994; Griffin, et al. 1995; Griffin, et al. 1998; Royston, et al. 1999; Mrak and Griffinbc 2001; Heizmann, et al. 2002).

There is an interest in S-100B as marker for brain injury. S-100B is released into the blood and cerebrospinal fluid after head injuries. Several attempts have been made to use it as a marker for the severity of the injury, for prognostication, and for support for the decision whether to hospitalise a person after mild and moderate head injury or not (Ingebrigtsen and Romner 2003; Raabe, et al. 2003; Savola, et al. 2004; Undén, et al. 2008). S-100B is not only found in the central nervous system, so injuries in other parts of the body can also influence the serum levels of S-100B (Anderson, et al. 2001a; Anderson, et al. 2001b; Undén, et al. 2004; Undén, et al. 2005).

The half time of S-100B is estimated to be 30 min – 2 hours (Usui, et al. 1989; Jönsson, et al. 2000; Ytrebo, et al. 2001; Townend, et al. 2006).

NSE

NSE is one of five isoenzymes of the glycolytic enzyme enolase. There a several dimeric isoenzymes with specific subunits (α, ß, and γ). The γγ and αγ isoenzymes are called NSE (Marangos, et al. 1979; Marangos, et al. 1980). It is located in the cytoplasm of the cell and also involved in increasing neuronal chloride levels during onset of neuronal activity (Johnsson, et al. 2000). Initially it was thought that NSE was found only in neurons but is has been shown that neuorendocrine cells, several non-neural and non-neuroendocrine cells contain NSE. NSE has been used as a marker tumour diseases such as small cell carcinoma of the lung and neuroblastoma (Carney, et al. 1982; Springall, et al. 1984; Zeltzer, et al. 1986). The concentration of NSE in CSF has been found to be changed following several neuronal diseases such as stroke, and Alzheimer's disease (Hay, et al. 1984; Cutler, et al. 1986; Persson, et al. 1987).

The biomarker has been investigated as an marker for TBI and as an predictor of outcome after TBI (Ergun, et al. 1998; Bandyopadhyay, et al. 2005; Naeimi, et al. 2006).

NSE has a estimated biological half-life of approximately 30 hours (Johnsson, et al. 2000),

AIMS

- To increase the understanding of the ICP targeted treatment used for sTBI.

- To evaluate the drift and reliability of the CMS device used during ICU treatment and further to study the correlation between ICP measured by the CMS device and the golden standard, ventriculostomy.

- To investigate the instantaneous and lasting effect of hemicraniectomy on the ICP in patients treated for TBI and in whom the ICP was refractory to treatment. Further to study whether there was a difference in clinical outcome between patients with sTBI in whom decompressive hemicraniectomy was performed due to therapy refractive ICP elevation and those who did not need a hemicraniectomy.

- To study the occurrence of subclinical epileptic seizures in patients during intensive care treatment for TBI and so to estimate the risk of secondary brain damage due to epileptic seizures.

- To study the effect of prostacyclin as an ad on treatment in the protocol guided therapy for sTBI by studying the changes in micro-circulation as measured by cerebral microdialysis. Further to study, the effect of prostacyclin on the clinical outcome and the possibility to use the L/P as a prognostic tool in sTBI.

- To examine the changes in S-100B and NSE over time in patients with sTBI and to investigate the prognostic value of S-100B and NSE in sTBI.

MATERIALS AND METHODS

General methods

ICP targeted therapy, the Umeå treatment protocol

The treatment protocol used for the treatment of sTBI in Papers II – V has in detail been outlined above (**see page 24, Figure 2**). Shortly, this treatment rests aggressive neurosurgery and on the four corner stones of the "Lund concept": firstly, the use of sedation, barbiturates, metoprolol and clonidine in order to reduce the stress response and to reduce the cerebral metabolism, secondly, the reduction of capillary hydrostatic pressure, thirdly, the aggressive maintenance of normo-volemia and colloid osmotic pressure, and lastly, the reduction of cerebral blood volume.

Monitoring

ICP was monitored in all patients. The Codman® ICP Monitoring System was used in almost all of the patients. Some patients had their ICP monitored via a ventriculostomy, then using the level of the external meatus as the reference point. The ICP was continuously registered. In all patients arterial blood pressure was continuously monitored and the CPP calculated (Marquette Solar, General Electric Medical Systems, Milwaukee, WI, USA). The reference level used for the blood pressure was the level of the right atrium

Follow – up

The clinical follow-up was made by independent staff using structured interviews. The clinical outcome is reported as GOS.

Patients and methods

All patients studied have been treated at the Department of Neurosurgery and the Intensive Care Unit of Umeå University Hospital. There have been no direct complications related to the interventions in these papers. Neither to the implantation of ICP monitors, microdialysis catheters, applications of EEG electrodes, the performance of hemicraniectomies nor to the use of prostacyclin. The ethics committee of the University of Umeå has approved the interventions in the studies as well as the procedure of informed consent used in the interventional study on unconscious patients. The Läkemedelsverket (Medical Products Agency) has approved the pharmacological study of prostacyclin. No mortality or morbidity has been caused by the interventions reported.

Paper I

One hundred and twenty-eight prospective patients subjected to neurointensive care and in whom the ICP were monitored using the Codman® ICP Monitoring system with the CMS were collected between May 1998 and December 2003.

The CMS was implanted and calibrated according to the manufacturer's instructions. The procedure could take place in the operating theatre, the ICU, the emergency room, or in the radiology department.

After a small skin incision, approximately at the point of Kocher, a small burr hole (3 mm) was placed, where after the dura and cortex was coagulated. The CMS was then passed under the skin to a separate skin incision. The tip of the CMS was just submerged in saline and the system was calibrated. The calibration number given was noted and the CMS was introduced approximately 2 cm into the brain. The incision was then closed and the CMS fixed to the skin.

After ex-plantation of the CMS the sensor tip of the catheter was just submerged in saline and the pressure registered noted. The noted value is defined as the drift.

In 22 patients ICP was monitored concurrently by a ventriculostomy and a CMS. The ICP registered by the two methods was simultaneously measured and collected at random points in time.

Papers II -- V

Paper II is a retrospective paper of patients treated for TBI at our Department between January 1998 and December 2001. Paper III – V are prospective studies. Eligible for the study in Paper III were patients treated between March 2004 and September 2006. In Papers IV and V the patient material is the same. The study was a prospective consecutive randomised double blinded study of the effect of epoprostenol versus placebo in patients with sTBI, performed between January 2001 and December 2005.

In papers II – V the basal patient inclusion and exclusion criteria were very much the same.

The patients had to have had a verified head trauma. In Paper II, IV and V the patients should have had a level of consciousness of GCS 8 or less at intubation and sedation. In Paper III the patients should have been in need of cerebral intensive care for the TBI irrespectively of initial GCS. The age at inclusion in Papers II, IV, and V should be in the range of 15 -70 years and in Paper III 15 – 80 years. Patients with GCS 3 and or bilateral, dilated and fixed pupils were included. Exclusion criteria were: a first recorded CPP < 10 mmHg (dead on arrival), arrival in our department > 24 hours after trauma, and penetrating head injury. In Papers IV and V additional exclusion criteria were pregnant or lactating woman, known bleeding diathesis, and known allergy to epoprostenol. The patients should be in need of cerebral intensive care for more than 72 hours. Those who could be discharged within 72 hours of trauma were not regarded to have a sTBI even though their initial GCS were ≤ 8.

Patients dead within the three first months after the trauma were regarded as mortality due to sTBI (including those dead within 72 hours).

Paper II

For this paper the ICP, MAP, and CPP were collected hourly from all patients treated for TBI and fulfilling the inclusion criteria. The patients who had undergone DC were identified. The data from these patients were then compared with the data from the patients who did not need a craniectomy.

The indication for DC was a ICP that could not be brought under control by the earlier steps in the treatment guidelines. Before the DC, the given therapy was evaluated and a new CT scan of the brain performed. The decision whether to perform a uni- or bi-lateral DC and on which side to operate was based on the CT-scan. The craniectomy should measure not less than 12 x 8 cm and a dura plasty not smaller than 4 x 10 cm should be made (**Figure 5**).

Figure 5
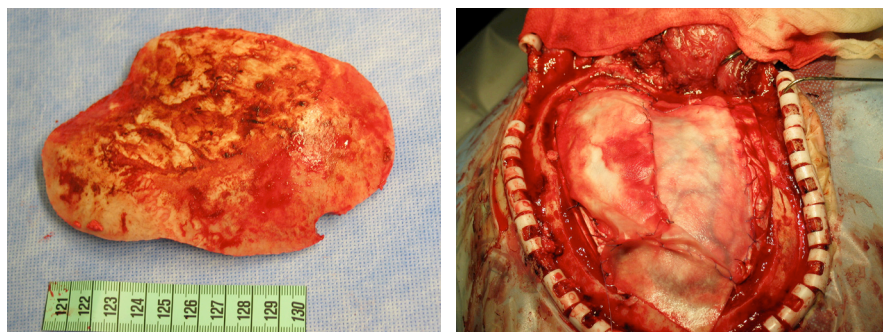
Decompressive craniectomy, the bone flap and the dura plasty.

Paper III

For the EEG monitoring two NicoletOne Monitors (VIASYS Healthcare Inc.) was used. Trained neurophysiological technicians placed five needle electrodes subcutaneously at F3, F4, P3, P4, and a midline reference (**Figure 6**). Raw EEG was continuously displayed at the bedside of the patient F3 - P3 and F4 – P4 tracings. The sensitivity was set at 100 μV per cm and filter settings at 0,5 – 70 Hz. Senior neurophysiologists analysed the trends at least two times a day. They also reviewed samples of the raw EEG, often using a higher sensitivity (50 μV/cm) and in reference derivations. No systematic search for epileptic interictal discharges or nonspecific slowing was done.

During the ICU time the patients did not receive any prophylactic anti-epileptic drugs. The data of drugs and fluid administration to the patients was stored in a computer system (Picis, Picis Inc.).

Figure 6
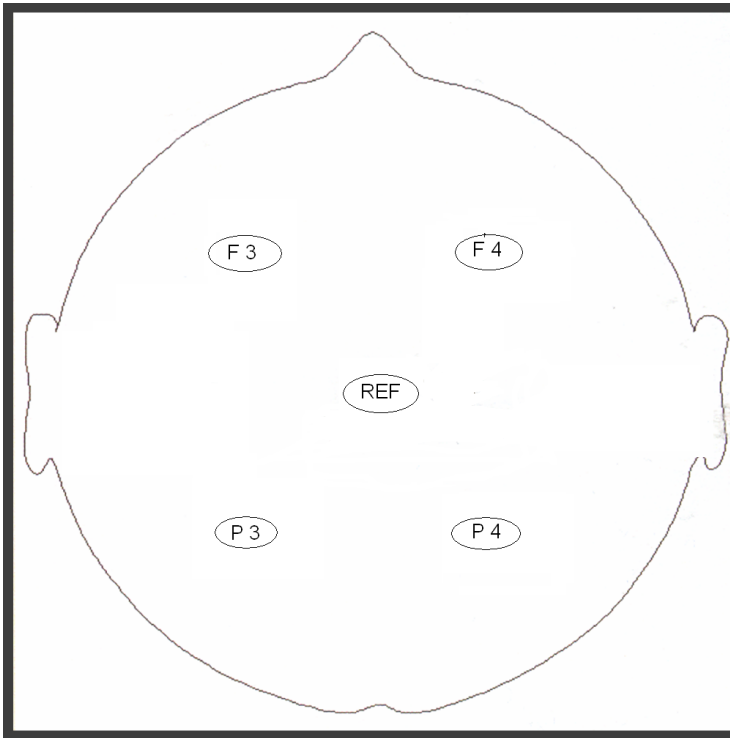
Schematic view over the placement of the EEG needle electrodes.

Papers IV and V

Microdialysis

The patients received three microdialysis catheters, as soon as possible after admission and inclusion in the study. Two gold tip microdialysis catheters (CMA 70, CMA Microdialysis AB, Solna, Sweden) were placed intracerebrally in a standardised way, bilaterally and frontally, approximately at the point of Kocher. The two cerebral microdialysis catheters were designated A and B. The A catheter should be placed in the most injured hemisphere as judged from the CT scans. A third microdialysis catheter (CMA 60, CMA Micordialysis AB) was placed subcutaneously in the adipose tissue in the upper part of the abdomen. All the microdialysis catheters were perfused at a flow rate of 0,3 μl/min, using the "Perfusion fluid CNS" in the cerebral catheters and "Perfusion fluid T1" in the subcutaneous catheter (CMA Microdialysis AB). The sampling started after 0,5 – 2,5 hours after the start of the microdialysis, as the first dialysate was discharged. The sampling interval was 2 hours. The first sample was collected as zero – sample (0-sample, baseline). The samples were stored in a refrigerator for not

more than 24 hours after which they were frozen to -70°C. The microdialysis samples were analysed using a CMA 600 analyser (CMS Microdialysis AB).

Test drug

The patients were randomised to treatment with epoprostenol (Flolan®, Glaxo Smith-Kline) or placebo. The study was blinded for the investigators, treating physicians, ICU nurses, subjects, and their relatives. The test drug was given as an infusion at a rate corresponding to a dose of 0,5 ng/kg/min for 72 hours and then tapered over the following 24 hours. The test drug was started at the same time as the microdialysis 0-sample was changed.

S-100B and NSE

As soon as possible after the arrival of the patient the first blood sample for analysis of S-100B and NSE was drawn. Blood samples were taken twice a day for the first five days of treatment. The sera were stored in a -70°C refrigerator. The fully automised LIASON® system was used for analysis. For S-100B the LIASON Sangtec 100 assay was used and for the NSE the LIASON NSE assay (AB DiaSorin, Sangtec Medical, Bromma, Sweden). The analysis was made using duplicate values.

Statistics

The data were transferred to, stored in, and analysed on a personal computer, using JMP™ v.5.0. (SAS Institute Inc) and MedCalc® version 9.6.00. For continuous variables results are reported as mean ± standard error of the mean (SEM) and for discrete variables as median and range. Two-sided Student's t-test paired or unpaired was used when appropriate for continuous variables and for discrete data Wilcoxon signed rank test. Analysis of variance was used when several continuous values were compared at the same time. For proportions the χ^2 was used. When indicated correlations were used. Logistic regression with ROC curve analysis was used to test for predictability. A $p \leq 0,05$ was considered statistically significant.

Results

Paper I

Figure 7 shows the drift over time in the 128 CMS devices. The mean drift was $0,9 \pm 0,2$ mmHg in a mean registration time of $7,2 \pm 0,4$ days ($1 - 16$ days). The drift was 0 in 25% of the devices and ± 2 mmHg in 79%. There was no correlation found between time and drift. The ICP in 22 patients measured simultaneously at 469 randomly selected points is depicted in **Figure 8**. The correlation was good (r = 0,79, p < 0,0001). The mean ICP measured by CMS and the ventriculostomy was $19 \pm 0,2$ mmHg and $18,3 \pm 0,3$ mmHg, respectively. No complications related to the CMS device such as haemorrhages or infections were seen.

Figure 7
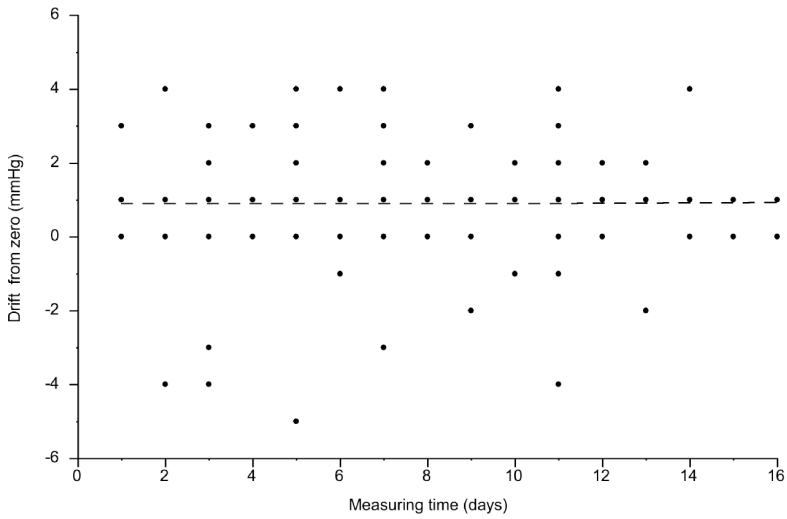
The drift over time in 128 Codman MicroSensors™.

Figure 8
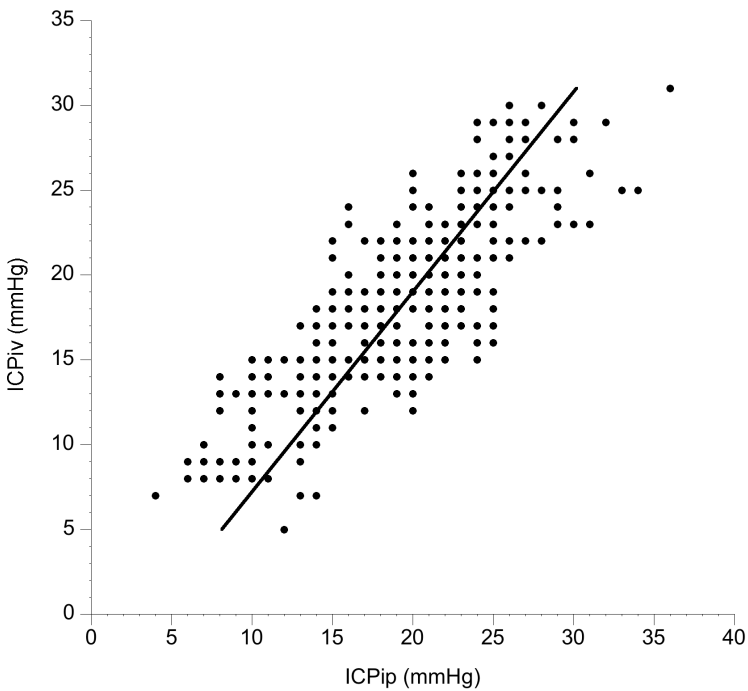
The correlation between ICP measured by the Codman MicroSensor™ (ICPip) and ventriculostomy (ICPiv) (r = 0,79, p < 0,0001).

Paper II

Ninety-three patients (71 males, 22 females) with a mean age of 37,6 ± 1,7 years and a median GCS of 7 at intubation and sedation met the inclusion criteria. In 21 of these patients (23%) DC was performed. The mean treatment time in the ICU before DC was 45 hours. Statistically there was no difference between the DC group and the non-craniectomised (NCD) group in regard to sex, age, or initially GCS.

The mean area of the DC in patients who underwent uni-lateral procedures was 88 ± 7 cm² corresponding to a calculated volume gain of 98 ± 11cm³. In patients with bi-lateral DC the area of decompression was 150 ± 14 cm² and the calculated volume gain 154 ± 20 cm³.

Just before the DC the ICP was 36,4 ± 3,4 mmHg and just after DC 13,1 ± 2,1 mmHg (p < 0,001 ANOVA, p < 0,001 post hoc). The ICP reduction was still statistically significant 72 hours after the DC (p < 0,001 post hoc) (**Figure 9**).

There was no statistically significant difference between the DC-group and the NCD-group in favourable outcome (GOS 4-5) (**Figure 10**).

Figure 9
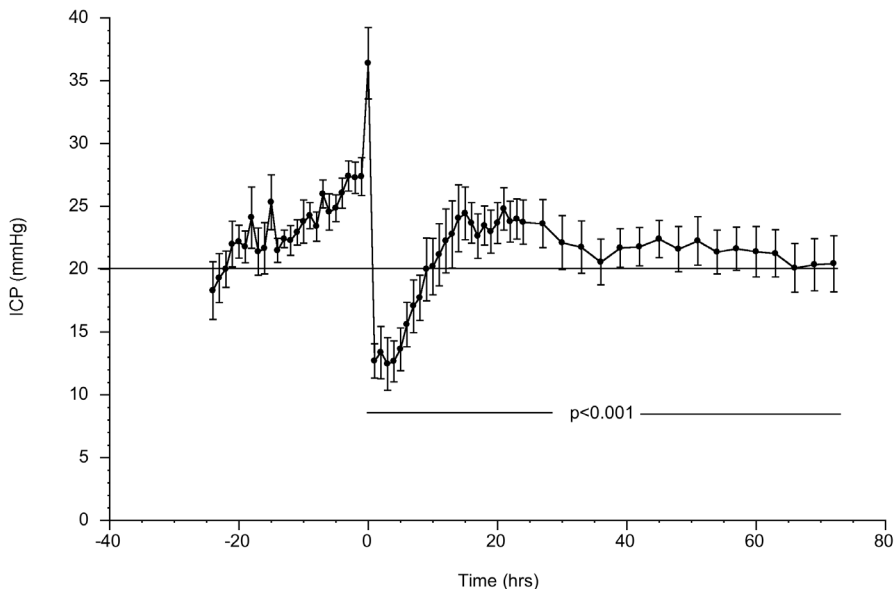
The mean ICP in the patients treated with decompressive hemicraniectomy from 24 hours before the procedure till 72 hours after (bars indicate SEM)

Figure 10
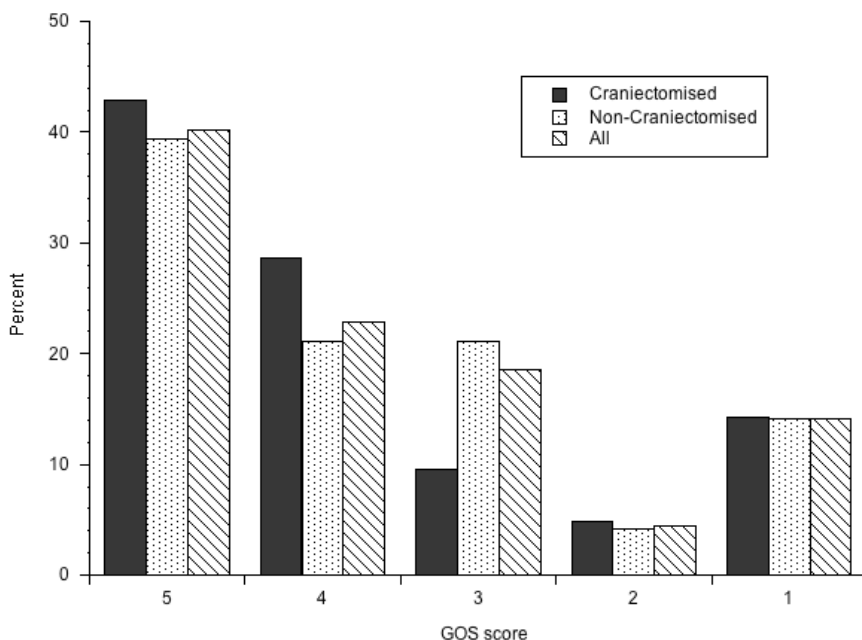
Outcome as GOS in craniectomised and non-craniectomised patients, and all.

Paper III

Forty-seven patients (33 men, 14 women) were included with a mean age of 40 ± 2,5 years, and a median GCS at intubation and sedation of 6 (range 3 − 15).

EEG was recorded for 7 334 hours (~ 306 days). The mean registration time was 156 ± 11 hours and the registration started at a mean of 51 ± 5 hours after admission (**Figure 11**).

During the registration no seizure was recorded, neither clinical nor electroencephalographic. Clinical seizures were observed in 4 patients (8,5%) before the start of the monitoring. All of this seizures occurred before sedation and intubation.

The patients were all sedated using midazolam, propofol, thiopental or combinations thereof (**Figure 12**). In only eight of the patients parts of the registration was done without sedation, and then at the end of the registration period.

Paper IV

Forty-eight patients (31 males, 17 females) with a median GCS at intubation and sedation of 6 and a mean age of 35,5 ± 2,2 years participated in the study. 23 patients were included in the epoprostenol group (PG-G) and 25 in the placebo group (Plac-G). There were no statistically significant differences between the groups in

Figure 11
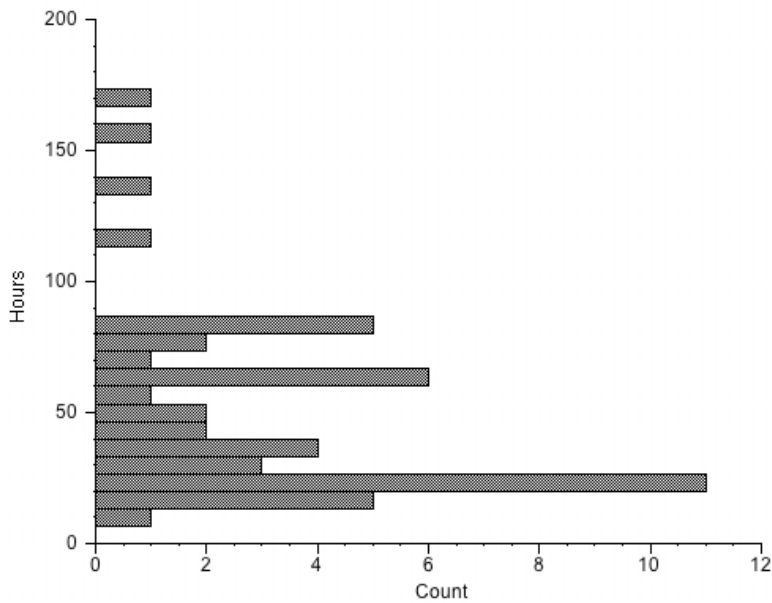
Time from admittance to Umeå University Hospital to start of the EEG registration.
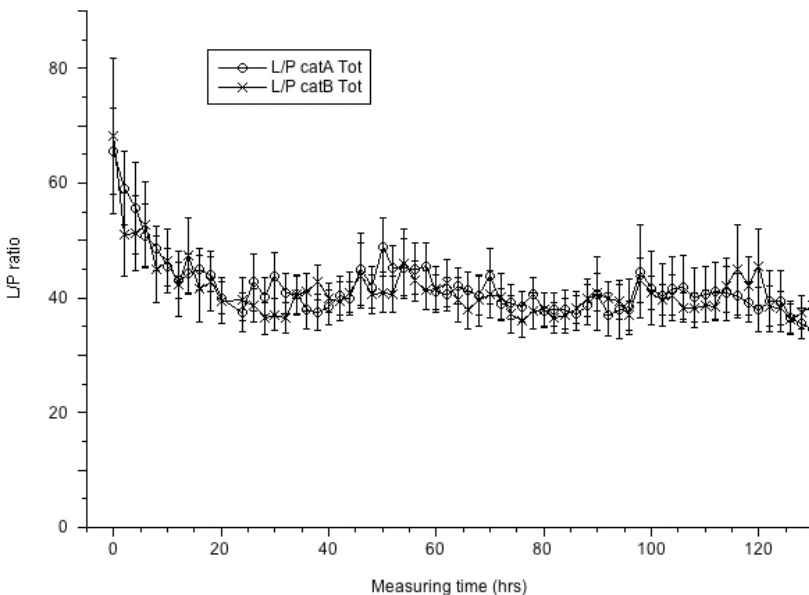
Figure 12
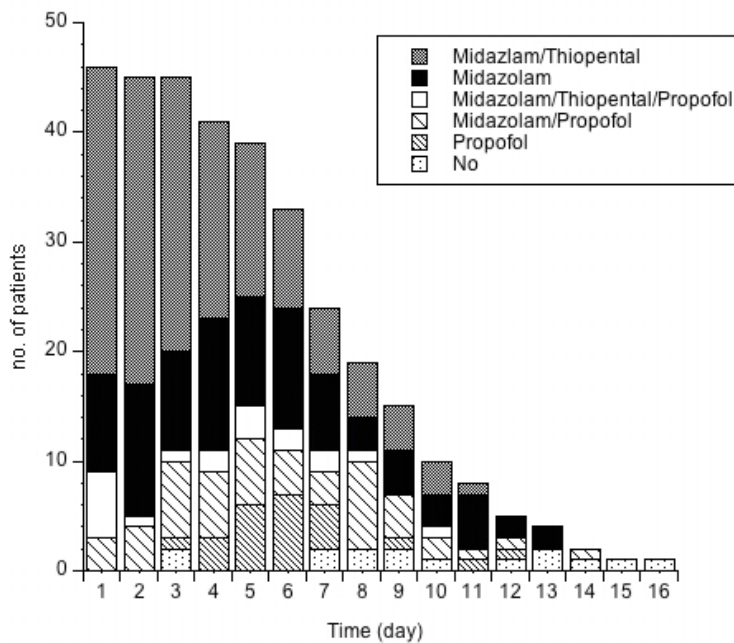
The daily use of sedatives during continuous EEG registration.

regard to sex, age, GCS, and time between accident and implantation of the micro-dialysis catheters. More than two thirds of the patients (68,7%) were multi-trau-matised.

ICP, MAP and CPP were followed over time and there were no statistical signifi-cant differences between the PG-G and the Plac-G.

The L/P of the 0-sample was evidently higher than the supposed normal value. There was a clear reduction in L/P comparing the 0-sample with the sample at 24 hours in both catheters, though only the reduction in the A-catheter was statistically significant. There was no statistical difference in L/P between the PG-G and Plac-G at 24 hours of treatment or in the relative decrease between the 0-sample and 24 hours. The L/P decreased over time. **Figures 13** and **14** depict the changes in L/P over time, for the total material and for the different catheters and treatment groups.

Figure 13

The mean lactate pyruvate ratio in the intracerebral microdialysis catheters
*(Catheter A worse side, Catheter B better side, bars indicating the SEM).*

Figure 14
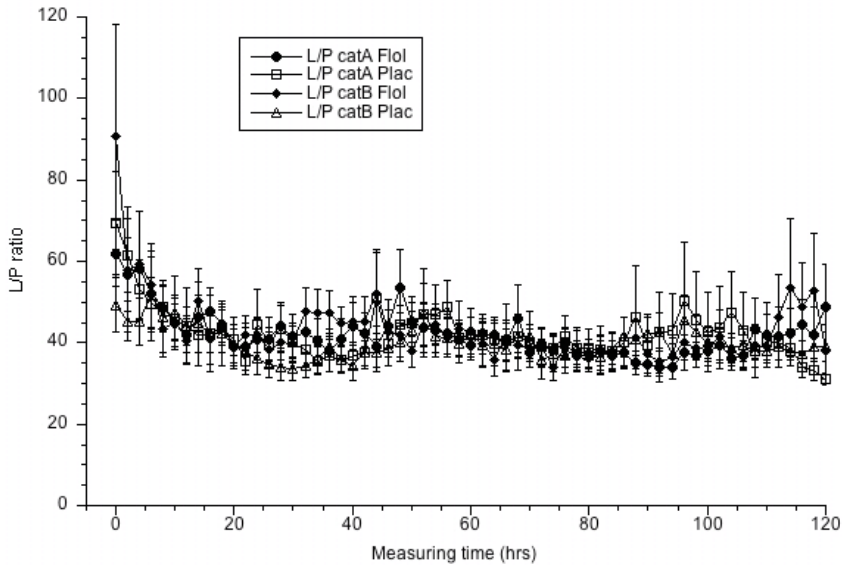
The mean lactate pyruvate ratio in the intracerebral microdialysis catheters, divided in worse (catheter A) side, better side (catheter B), epoprostenol group (Flol) and placebo group (Plac), bars indicating SEM.

The favourable outcome (GOS 4- 5) at 3 months follow-up was 52% and the mortality was 12.5%. No statistical significant difference was found between the treatment groups (**Figure 15**). The favourable outcome would be 61% if patients with an initial GCS of 3 and / or bilateral dilated and fixed pupils would be excluded. The mortality then would be 0%.

There was no statistical significant correlation between the initial L/P and the GOS at 3 months, or the GOS dichotomised in favourable (GOS 4 – 5) and unfavourable (GOS 1-3), or GOS dichotomised in favourable (GOS 4-5), unfavourable (GOS 2 – 3), and mortality (GOS 1).

In a ROC curve analysis of the 0-sample and the dichotomisation dead or alive the AUC was 0,701 (CI 0,556 – 0,835) and the cut-off value of 110 (sensitivity 60%, specificity 87,5%). If the first L/P is to be used for the prediction of death (i.e. to treat or not) assuming that the test must have a 95% specificity, i.e. 1/20 of the salvageable patients is left to die, the cut off value of the L/P would be 137 and the sensitivity 20%.

Figure 15
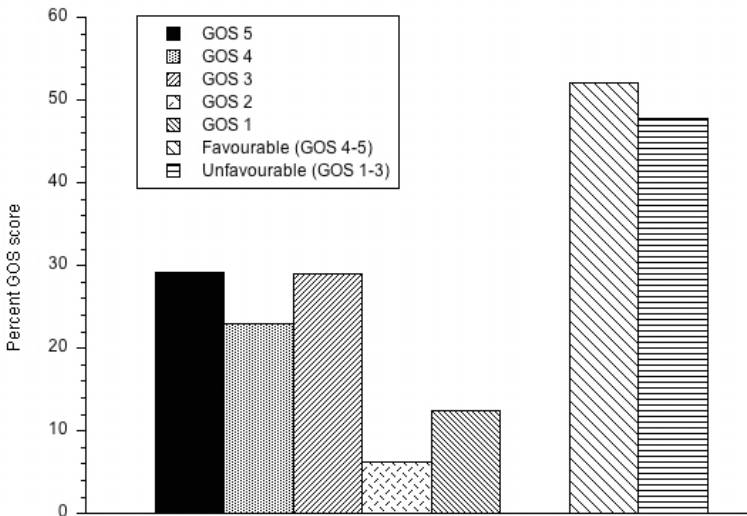
*Outcome as GOS in 47 patients treated for severe traumatic brain injury.*

Paper V

The first sample for analysis of S-100B and NSE was collected at mean 15,6 ± 1,4 hours after injury (range 6 -37 hours). In the first sample the mean concentrations of S-100B and NSE were 1,04 ± 0,21 µg/l, and 18,94 ± 2,32 µg/l, well above the normal value which is < 0,2 µg/l for S-100B and 10µg/l for NSE (Nygaard, et al. 1998).

Figure 16 shows the decrease in S-100B and NSE levels over time. In the first sample there was a statistically significant higher concentration of S-100B and NSE in the patients with GCS 3 and GOS 1 as compared with the patients with GCS 4-8 and GOS 2-5, respectively (**Figures 17** and **18**). There was a statistically significant correlation between the two biomarkers and ICP (S-100B: R =0,75, p < 0,0001; NSE: R = 0,51, p < 0,0001).

A ROC curve analysis of the initial concentration of the biomarkers and outcome shows when outcome was dichotomised in favourable (GOS 4 - 5) and unfavourable (GOS 1 – 3) that the AUC was near to 0,5 for both the markers. If the dichotomisation is made dead or alive the AUC was 0,69 and 0,73 for S-100B and NSE, respectively. Using this analyses to predict whether to treat or not and allowing for that 1/20 of the patients whom would have been salvageable was left to die the cut off level for S-100B would be 1,67 µg/l and for NSE 47,15 µg/l.

A good statistical significant correlation was found between the to biomarkers (R = 0,63, p ≤0,0001).

Figure 16
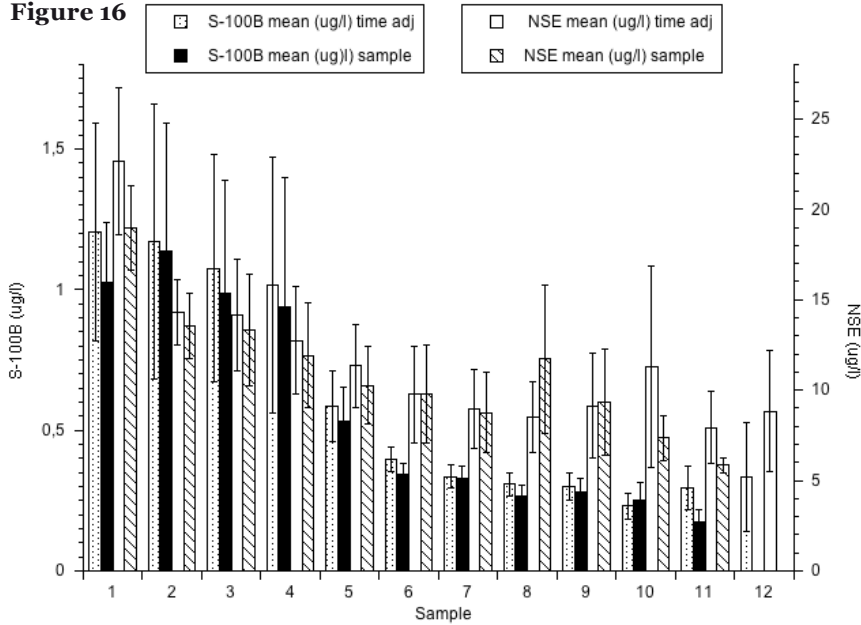
The mean S-100 and NSE concentrations over time. Indicating concentration samples for sample and in time adjusted samples (samples grouped in the nearest 12 hours period after trauma, bars indicating SEM)

Figure 17
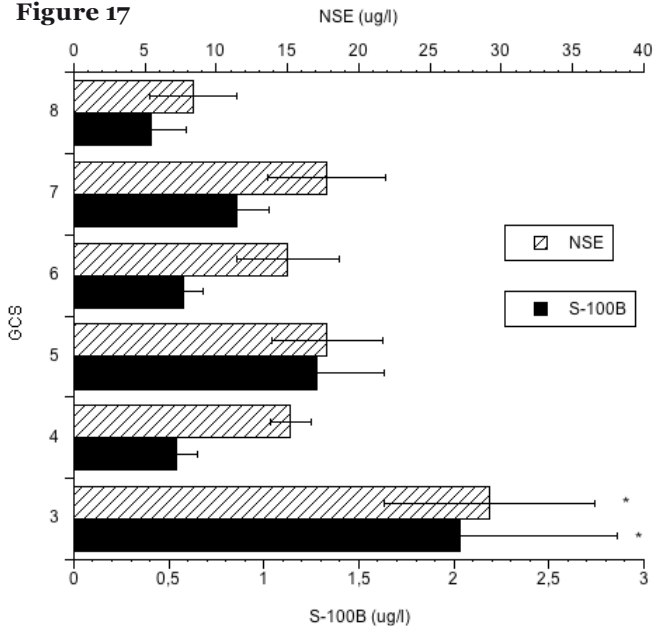
*The mean intial S-100B and NSE concentration in relation to GCS at intubation and sedation (bars indicating SEM, * = p ≤ 0,01 ANOVA with post hoc test).*

Figure 18
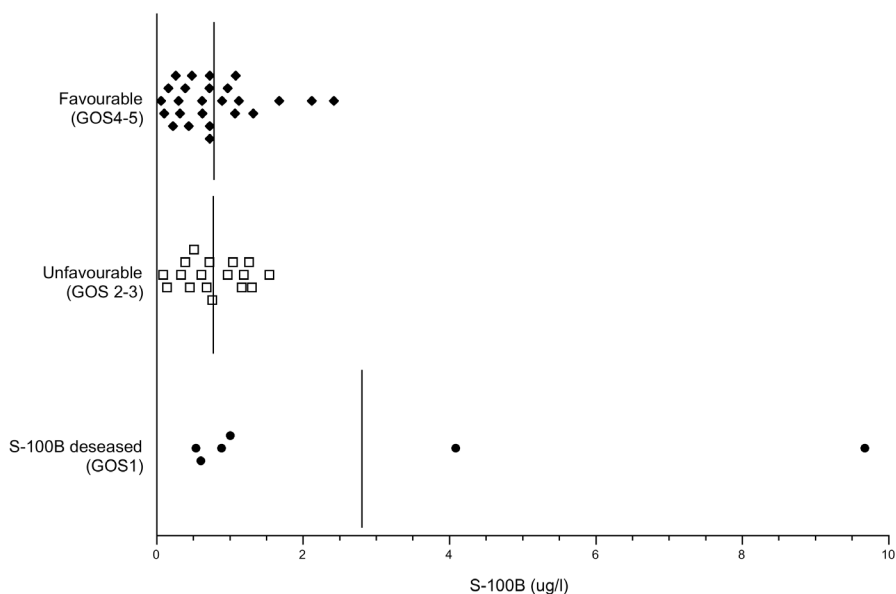
The initial S-100B concentration in relation to clinical outcome (GOS).

Discussion

Paper I

The drift in the Codman® ICP Monitoring System is less than 1 mmHg over 7 days. These findings confirm earlier reports in much smaller studies that the drift in the CMS is very low (Gopinath, et al. 1993; Fernandes, et al. 1998; Morgalla, et al. 2001). There has been a concern about the drift in the CMS device since it not can be re-calibrated after insertion. The data suggest that the CMS system is stable over time with little drift.

The conformity between the CMS and the ventriculostomy was shown to be good. Similar findings have been reported by Gopinath and colleuges (Gopinath, et al. 1993). Lenfeldt and colleges have reported a very good correlation between the intraparenchymal ICP measured with the CMS and lumbar intrathecal pressure measured with a fluid filled transducer technique (Lenfeldt, et al. 2007). The good concordance of ICP measured with ventriculostomy and the CMS is confirmed by a Bland Altman plot analysis.

These are important findings as the reliability of the ICP monitoring is a corner stone in the treatment and monitoring of the sedated patient with sTBI. The findings are further important, as the therapy used in these patients is an ICP targeted therapy and changes of treatment are often based or initiated by changes in the ICP. The robustness of the CMS system is shown as at least 10 colleagues have been involved in the implantation and managing of the systems. The CMS has several advantages compared with the traditional ventriculostomy and fluid pillar based measuring system. It is easier to insert, can be inserted literally anywhere in the hospital, is much easier to handle during transportation of the patient, and there is very few complications related to the use of the CMS.

Paper II

Recently there have been several reports on the effects of DC (Gaab, et al. 1990; Guerra, et al. 1999; Meier, et al. 2000; Münch, et al. 2000; Hejazi, et al. 2002; Kontopoulos, et al. 2002; Hutchinson, et al. 2006; Hutchinson, et al. 2007; Howard, et al. 2008; Timofeev, et al. 2008). However, many of the publications do not describe the procedure, the size of DC, the ICP changes over time, or the treatment protocol used. In the present study a statistical significant reduction of ICP was showed to be achieved from just before to just after DC. After this initial reduction there was an increase in ICP over the first 12 – 24 hours after which the ICP levels out at an acceptable level. The reduction of ICP was still statistically significant for the 72 hours following the DC. During this time the cerebral intensive care was carried on using the Umeå guidelines for sTBI. There are only three earlier reports making the same observation of an increasing ICP after an the initially achieved decrease of the ICP after DC (Whitfield, et al. 2001; Hejazi, et al. 2002; Schneider, et al. 2002). The explanation for this increase in ICP after DC can be an increased oedema formation due to the brain's altered physiological environment. The size of the DC is of great importance, and it is necessary to perform a dura plasty to allow for maximal expansion of the brain. Calculations of the size of the craniectomies performed and the volume gained by the procedure was performed. Only one report in the literature was found to report of the craniectomy size (Münch, et al. 2000). One could expect that the results in the DC group should be worse than in the non-DC group. The mortality and the favourable outcome (GOS 4 – 5) found did not statistically significant differ between the two groups. In the literature mortality between 14,7 – 55 % and a favourable outcome (GOS 4 – 5) of 26 – 66% have been reported in DC patients (Gaab, et al. 1990; Polin, et al. 1997; Meier, et al. 2000; Kontopoulos, et al. 2002; Meier and Grawe 2003; Howard, et al. 2008).

The conclusion is that the DC is an important step and a valuable tool in a protocol guided ICP targeted treatment for sTBI. DC can interrupt a malignant development in ICP. The DC is a worthwhile procedure as the outcome is as good as in the non-DC patients.

Paper III

In contrast to the to the general conception that nonclinical seizures are common in patients who are subjected to cerebral intensive care (Jordan 1993; Vespa, et al. 1999; Towne, et al. 2000; Claassen and Mayer 2002; Claassen, et al. 2004; Ronne-Engström and Winkler 2006) no clinical or EEG seizures was found during 7334 hours of monitoring in patients with TBI. There are two papers reporting on seizures in TBI patients subjected to neuro-intensive care (Vespa, et al. 1999; Ronne-Engström and Winkler 2006). Other papers are reporting heterogeneous materials. Vespa and co-workers reported of 22% clinical and EEG seizures in their material. The corresponding frequency of seizure reported by Ronne-Engström and Winkler was 28% EEG seizures in 70 patients. In neither of the two reports even though both papers report the use of protocol guided treatment, it is not clear if and how the patients were sedated, though all of them were ventilated. Vespa et al. used prophylactic anti-epileptic medication in all of the reported patients. One of the reasons that no clinical or subclinical seizures were found in the present study could be that during almost all of the registration time the patients were sedated. Awakening tests are not used in the Umeå treatment guidelines. Such tests, could from a theoretical point of view, provoke seizures by inducing stress to the patients. There have been reports of worse outcome in patients with subclinical seizures during cerebral intensive care (Young, et al. 1996; Chiaretti, et al. 2000). These finding have been explained by secondary injuries to the brain caused by increased metabolic demands of the brain caused by the seizures. The results indicate that the protocol guided treatment used for TBI protects the patients from this risk of secondary brain injuries.

Paper IV

No statistically significant difference of the L/P at 24 hours of treatment could be shown in the group treated with epoprostenol in the dose of 0,5 ng/kg/min as compared with the placebo group.

From a theoretical point of view there are indications for the beneficial use of PGI_2. In the healthy person there is a balance between PGI_2 and TXA_2. In the traumatised person this balance is shifted towards TXA_2 (Gryglewski, et al. 1978; Moncada and Amezcua 1979), and thus lead to vasoconstriction, platelet aggregation, and leukocyte adhesion and so to impaired microcirculation. The endogenous production of PGI_2 has been reported to be in the range of 0,08 – 1 ng/kg/min (Lewis and Dollery 1983; Ritter, et al. 1983; Davies and Hagen 1993). Grände et al showed in 2000 that PGI_2 given to patients with sTBI seemed to have an effect on the microcirculation as measured by microdialysis (Grände, et al. 2000). The dose used by Grände was 0,5 – 1 ng/kg/min. One can speculate that the dose used in the present study was to low. The dose was chosen based on the study by Grände and the safety

study previously performed (Naredi, et al. 2001). There could in spite of the present results be other beneficial effects of PGI_2, such as effects on the cardiovascular and respiratory stability of the patients, on the cognitive outcome, or on the functional outcome of the patients. These questions have to be subject to further studies.

The L/P decreased over time as earlier described (Persson and Hillered 1992; Ståhl, et al. 2001). It was still elevated over the presumed normal value of 20 (Reinstrup, et al. 2000; Schulz, et al. 2000) after 120 hours. Other authors have indicated that a more appropriate cut-off level of the L/P would be 40 (Vespa, et al. 2005; Vespa, et al. 2007). This is supported by a publication from Umeå, where a level of 40 was found in awake patients (Ågren-Wilsson, et al. 2005).

An important finding is that the L/P can not be used as a surrogate endpoint for clinical outcome as no statically significant correlation between the initial L/P and the clinical outcome at 3 months measured as GOS was found. Further, the L/P could not prognosticate for death and so could not be used as the argument on which to base the decision whether to treat or not. This finding is supported by Nelson et al. (Nelson personal communication).

The outcome reported in this study is less favourable than have been reported earlier from Umeå (Naredi, et al. 2001; Wahlström, et al. 2005; Olivecrona, et al. 2007). One reason for this could be that the GOS is reported at 3 months after the injury, which is much earlier compared with the other studies which have a later follow-up. Another explanation is that the patients in the present study are more severely injured as compared with our previous studies. However, the results are still among the best reported in the literature.

The results of this study indicate that the clinical value of the microdialysis must be questioned. There is no support for using the L/P for prediction of outcome or for the decision to treat or not.

Paper V

As expected an elevated concentration of the biomarkers was found in the initial sample. The time profiles of the individual S-100B samples indicate that the biological half-time seems to be much longer than the reported half-time of between 0,5 and 2 hours (Usui, et al. 1989; Jönsson, et al. 2000; Ytrebo, et al. 2001; Townend, et al. 2006). The interpretation of this would be that the earlier reported half-times are not correct or that there is an ongoing release of S-100B from the injured brain over time, an explanation also discussed by Raabe and co-workers (Raabe, et al. 1999b).

A significant correlation between ICP and the biomarkers over time was found. Similar findings have also been reported in an experimental pig model (Ytreboo, et al. 2000).

There have been several reports stating that the initial S-100B and NSE value would predict for clinical outcome measured as GOS at 3 months after injury (Wo-

ertgen, et al. 1997; Raabe, et al. 1999a; Raabe, et al. 1999b; Rothoerl, et al. 2000; Vos, et al. 2004). In the present study the initial value of the biomarkers can predict for outcome dichotomised as dead or alive but not for favourable and unfavourable outcome. One explanation for this could be that many of these reports on the prognostic value of S-100B are based on samples drawn earlier after injury than ours. Using time adjusted values did not increase the prognostic precision of S-100B. Based on a ROC curve analysis the predictive value of both biomarkers for the decision to treat or not to treat has to be regarded as weak. These findings are partly supported by Nylén et al 2008 and by Undén et al 2007 (Undén, et al. 2007; Nylen, et al. 2008).

Much of the discussion in the literature concentrates around S-100B even when NSE is simultaneously measured. Actually, it was found in the present study that NSE is as good as S-100B. As NSE is less sensitive to the time elapsed from the trauma till the sampling it would perhaps be more appropriate to use NSE as a biomarker for the prediction in sTBI.

Summary of the thesis

Patients with sTBI are treated in a protocol guided manner. The protocol used is based on the "Lund concept". The treatment is based on aggressive neurosurgery and physiological principles, fore most on the regulation of fluid transport or flux over the BBB. The aim of the treatment is a normalisation of the ICP.

This means that the monitoring of the ICP is an essential part in the treatment protocol and many treatment decisions are based on the changes in ICP. Further, the ICP monitoring is the most important way of monitoring the patients' cerebral condition as no awakening tests are done. The results show that the CMS used for monitoring of the ICP is a reliable tool for ICP monitoring. It is demonstrated that the CMS has a low drift over time, and that the pressures measured with the device is in agreement with the ICP measured by ventriculostomy. Further, a low rate of complications is found. The conclusion drawn is that the CMS can safely and preferable be used for monitoring of the ICP.

DC achieves an immediate decrease in ICP , which under ongoing neuro-intensive care is lasting over time. A malignant increase in ICP can so be interrupted. The clinical outcome achieved in the patients in whom one has been forced to operate on with a DC is as good as in the patients in whom the ICP could be brought under control without DC. DC can therefore be considered as a valuable tool for the interruption of a malignant development of the ICP. The study also confirms the role of DC in the used treatment guidelines.

No subclincal or clinical epileptic seizures during the time of neuro-intensive care for TBI were observed. This indicate that the used protocol, with continuous sedation, protects the patients from a possible cause of secondary brain injuries, i.e.

increased metabolic demand due to seizures. This can be a contributing reason for the good results reported.

No evident effect of epoprostenol on the L/P as a surrogate measure of improved microcirculation was seen. The prognostic value of the L/P was low and can not be used in the decision whether to treat or not. The clinical outcome at 3 months was not changed by epoprostenol.

The initial levels of the biomarkers, S-100B and NSE, were elevated and decreased over time. There was a significant correlation between the biomarkers and GCS 3 and GOS 1. A further analysis of the predictive value of the biomarkers for the decision to treat or not, showed that the biomarkers can not be used for this purpose with a high clinical reliability.

Conclusion

The ICP targeted protocol guided treatment used in Umeå is a reliable treatment protocol. The ICP measuring device used for the monitoring is reliable and safe. The use of DC has indicated its place in the treatment algorithm. The protocol seems to safeguard the patients from secondary brain injuries. Epoprostenol, in the used dose, does not have any beneficial effects on the microcirculation as measured by intracerebral microdialysis. The use of microdialysis and brain injury biomarkers does not seem to improve the possibility to prognosticate for outcome. The clinical importance of cerebral microdialysis and biomarkers are of doubtful value in the decision making process in the treatment of patients with sTBI. Microdialysis is still a valuable research tool. The treatment steps in the used guidelines seem to be adequate. The clinical outcome in sTBI treated by this protocol is as good as any other published results in the world.

SAMMANFATTNING PÅ SVENSKA

Svår traumatisk skallskada är en betydande orsak till både död och bestående men. Vid Neurokirurgiska kliniken, Norrlands Universitetssjukhus, behandlas patienter med en svår skallskada med en intrakraniellt tryckstyrd terapi. Denna baseras på en agressiv neurolirurgi och vilka fysiologiska principer syftar till att optimera mirkocirkulationen i hjärnan och på så sätt förebygga eller förhindra s.k. sekundära hjärnskador.

Eftersom behandlingen inriktas på att normalisera det intrakraniella trycket är noggrannheten och tillförlitligheten hos det mätinstrument som man använder för att mäta det intrakraniella trycket av mycket stor betydelse. Därför studerades prospektivt noggrannheten, driften och komplikationerna till den använda tryckmätaren hos 128 patienter. Driften var $0,9 \pm 0,2$ mmHg under en medelregistreringstid på $7,2 \pm 0,4$ dagar. I en vidare analys jämfördes slumpmässigt värden på det intrakraniella trycket hos 22 patienter hos vilka trycket mättes samtidigt med tryckmätaren och genom en ventrikulostomi. Dessa värden överensstämde mycket väl. Inga kliniskt signifikanta komplikationer till tryckmätaren noterades.

1997 introducerades uni- eller bilateral hemikraniektomi, kirurgiskt avlägsnande av skalltaket med duraplastik, i behandlingsprogrammet. Effekten av hemikraniektomi studerades retrospektivt hos patienter vårdade 1998 – 2001 för skallskada. Hos dem som opererades med hemikraniektomi var det intrakraniella trycket 36,4 mmHg precis före ingreppet och 12,6 mmHg omedelbart efter. Efter detta steg det intrakraniella trycket långsamt och planade ut strax ovan 20 mmHg. Det intrakraniella trycket var statistiskt signifikant lägre under de första 72 timmarna efter hemikraniektomi jämfört med precis före. Någon skillnad i det kliniska resultatet mellan de som genomgått hemikraniektomi och de som inte genomgått ingreppet i kunde inte påvisas.

Osynliga, subkliniska, epileptiska anfall har rapporterats vara vanliga hos patienter som behandlas för skallskada. Detta kan negativt påverka det kliniska resultatet av behandlingen eftersom anfallen kan ge upphov till sekundära hjärnskador. Därför studerades prospektivt förekomsten av epileptiska anfall hos patienter som behandlades för skallskada genom att kontinuerligt registrera EEG hos dessa patienter. Under 7 334 timmars registrering i 47 patienter kunde inte något epileptiskt anfall iakttagas eller återfinnas på EEG.

Teoretiskt och baserat på djurförsök skulle den kroppsegna substansen prostacyclin kunna förbättra mikrocirkulationen i hjärnan och på så sätt minska risken för sekundära ischemiska skador. Effekten av prostacyklin som ett tillägg till behandlingen undersöktes i en dubbel blind randomiserad prospektiv läkemedelsstudie. Den kommersiellt tillängliga substansen epoprostenol i en dos av 0,5 ng/kg/min användes. Effekten av prostacyklin studerades med hjälp av laktat-pyruvat kvoten uppmätt med intracerebrala mikrodialyskatetrar. Latkat-pyruvat kvoten är

ett mått på hjärnans metabolism. Det kliniska utfallet mättes tre månader efter olyckan. Fyrtioåtta patienter inkluderades i studien. Någon statistiskt signifikant skillnad i laktat -pyruvat kvot mellan den behandlade och icke behandlade gruppen kunde inte uppmätas efter 24 timmars behandling. Vid 3 månader var dödligheten 12,5% (95,8% utskrevs levande från intensivvårdsavdelningen) och 52% av patienterna hade återvänt till ett självständigt liv.

I samma studie undersöktes hjärnskademarkörerna S-100B och NSE. Halten av dessa i blodet följdes med blodprov 2 gånger om dagen under 5 dagar. Avsikten var att försöka uppskatta skadan och undersöka möjligheten att använda markörerna för att förutse det kliniska resultatet. Från början var halten av hjärnskademarkörerna ökad till patologiska nivåer, dessa sjönk sedan över tiden. Hos patienter som var helt reaktionslösa vid intubation och sedation och hos de som avled var halten av markörerna i det första provet signifikant förhöjt jämfört med de patienter som hade en bättre medvetandegrad eller som överlevde. En korrelation till det kliniska resultatet fanns men den kan inte användas för att förutse det kliniska resultatet.

Slutsatsen är att mätningarna av det intrakraniella trycket med hjälp av tryckmätaren är tillförlitliga, vidare att det använda behandlingsprotokollet är säkert och solitt. Epoprostenol i den givna dosen tycks inte ha någon effekt på de studerade mikrodialysparametrarna eller det kliniska resultatet. I svåra skallskador kan inte lakatat-pyruvat kvoten och hjärnskademarkörerna användas för att med tillräcklig säkerhet förutse det slutliga resultatet av behandlingen. De kliniska resultaten, som rapporteras är bland de bäst rapporterade i världen, med avseende på såväl återgång till självständigt liv som med avseende på dödligheten.

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