Severe Cerebral Emergency -
Aspects of Treatment and Outcome
in the Intensive Care Patient

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To Per, Oskar and Malin

Here comes the supernatural anaesthetist
If he wants you to snuff it
All he has to do is puff it
he’s such a fine dancer.

Genesis 1974
“The Lamb lies down on Broadway”
ABSTRACT
Severe Traumatic Brain Injury (TBI) and aneurysmal Subarachnoid Hemorrhage (SAH) are severe cerebral emergencies. They are common reasons for extensive morbidity and mortality in young people and adults in the western world. This thesis, based on five clinical studies in patients with severe TBI (I-IV) and SAH (V), is concentrated on examination of pathophysiological developments and of evaluation of therapeutic approaches in order to improve outcome after cerebral emergency.

The treatment for severe TBI patients at Umeå University Hospital, Sweden is an intracranial pressure (ICP)-targeted therapy according to “the Lund-concept”. This therapy is based on physiological principles for cerebral volume regulation, in order to preserve a normal cerebral microcirculation and a normal ICP. The main goal is to avoid development of secondary brain injuries, thus avoiding brain oedema and worsened microcirculation.

Study I is evaluating retrospectively 41 children with severe TBI, from 1993 to 2002. The boundaries of the ICP-targeted protocol were obtained in 90%. Survival rate was 93%, and favourable outcome (Glasgow Outcome Scale, score 4+5) was 80%.

Study II is retrospectively analysing fluid administration and fluid balance in 93 adult patients with severe TBI, from 1998 to 2001. The ICP-targeted therapy used, have defined fluid strategies. The total fluid balance was positive day one to three, and negative day four to ten. Colloids constituted 40-60% of total fluids given/day. Severe organ failure was evident for respiratory insufficiency and observed in 29%. Mortality within 28 days was 11%.

Study III is a prospective, randomised, double-blind, placebo-controlled clinical trial in 48 patients with severe TBI. In order to improve microcirculation and prevent oedema formation, prostacyclin treatment was added to the ICP-targeted therapy. Prostacyclin is endogenously produced, by the vascular endothelium, and has the ability to decrease capillary permeability and vasodilate cerebral capillaries. Prostacyclin is an inhibitor of leukocyte adhesion and platelet aggregation. There was no significant difference between prostacyclin or placebo groups in clinical outcome or in cerebral microdialysis markers such as lactate-pyruvate ratio and brain glucose levels.

Study IV is part of the third trial and focus on the systemic release of pro-inflammatory mediators that are rapidly activated by trauma. The systemically released pro-inflammatory mediators, interleukin-6 and CRP were significantly decreased in the prostacyclin group versus the placebo group.

Study V is a prospective pilot study which analyses asymmetric dimethylarginine (ADMA) concentrations in serum from SAH patients. Acute SAH patients have cerebral vascular, systemic circulatory and inflammatory complications. ADMA is a marker in vascular diseases which is correlated to endothelial dysfunction. ADMA concentrations in serum were significantly elevated seven days after the SAH compared to admission and were still elevated at the three months follow-up.

Our results show overall low mortality and high favourable outcome compared to international reports on outcome in severe TBI patients. Prostacyclin administration does not improve cerebral metabolism or outcome but significantly decreases the levels of pro-inflammatory mediators. SAH seems to induce long-lasting elevations of ADMA in serum, which indicates persistent endothelial dysfunction. Endothelial dysfunction may influence outcome after severe cerebral emergencies.

Key words: Severe traumatic brain injury, Intracranial Pressure-targeted therapy, albumin, prostacyclin, endothelial dysfunction, pro-inflammatory cytokines, Subarachnoid Haemorrhage, asymmetric dimethylarginine
ORIGINAL PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I  Wahlström MR, Olivecrona M, Koskinen LOD, Rydenhag B, Naredi S.  
Severe traumatic brain injury in pediatric patients: treatment and outcome using an intracranial pressure targeted therapy -the Lund Concept  
*Intensive Care Medicine* 2005; 31: 832-839

II Rodling Wahlström M, Olivecrona M, Nyström F, Koskinen LOD, Naredi S.  
Fluid therapy and the use of albumin in the treatment of traumatic brain injury  

III Olivecrona M, Rodling Wahlström M, Naredi S, Koskinen LOD.  
Prostacyclin treatment in severe traumatic brain injury. A microdialysis and outcome study.  
*Accepted for publication. Journal of Neurotrauma,* 2009. *Epub ahead.*

IV Rodling Wahlström M, Olivecrona M, Ahlm C, Bengtsson A, Koskinen LOD, Naredi S.  
Prostacyclin modulates the systemic inflammatory response in traumatic brain injury - a randomised clinical study  
*Submitted.*

V Rodling Wahlström M, Olivecrona M, Koskinen LOD, Naredi S, Hultin M.  
Subarachnoid haemorrhage induces a long-lasting increase of Asymmetric dimethylarginine (ADMA) in serum.  
*Submitted.*

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ABBREVIATIONS

ADMA  Asymmetric dimethylarginine
AIS   Abbreviated Injury Score
APACHE II  Acute Physiologic and Chronic Health Evaluation II
ARDS Acute Respiratory Distress Syndrome
BBB  Blood Brain Barrier
CBF  Cerebral Blood Flow
CBV  Cerebral Blood Volume
CNS  Central Nervous System
CPP  Cerebral Perfusion Pressure
CSF  Cerebrospinal Fluid
CT-scan  Computerised Tomography
CVP  Central Venous Pressure
DHE  Dihydroergotamine
ECG  Electrocardiography
EDH  Epidural Haematoma
EEG  Electroencephalogram
GCS  Glasgow Coma Scale
GOS  Glasgow Outcome Scale
Hb   Haemoglobin
H&H  Hunt and Hess grade
ICP  Intracranial Pressure
ICU  Intensive Care Unit
IL   Interleukin
ISS  Injury Severity Score
L/P  Lactate Pyruvate ratio
MAP  Mean Arterial Pressure
MODS Multiple Organ Dysfunction Syndrome
NO   Nitric Oxide
NOS  Nitric Oxide Synthase
RLS  Reaction Level Scale
SAH  Subarachnoid Haemorrhage
SAT  Oxygen saturation
SEM  Standard Error of the Mean
SD   Standard Deviation
SOFA Sequential Organ Failure Assessment
SDH  Subdural Haematoma
SIRS Systemic Inflammatory Response Syndrome
TBI  Traumatic Brain Injury
WBC  White blood cell
"Basic research has thus provided us and will continue to provide us with many new methods and technologies in medical care. These methods have to be constantly evaluated. This evaluation research, an aim of which is to discard old and less satisfactory methods and recommend the use and organisation of new techniques and procedures, should be an integral part of the clinical activity of our teaching hospitals."

Professor Emeritus of anaesthesiology
Martin H:son Holmdahl
Uppsala 2nd of June 1989

INTRODUCTION

Severe traumatic brain injury (TBI) and aneurysmal Subarachnoid haemorrhage (SAH) are severe cerebral emergencies with a high incidence of morbidity and mortality. TBI is the leading cause of mortality from trauma in the world. The incidence rate of TBI with a global perspective is estimated to 150-300 cases /100 000/year (Tagliaferri et al. 2006). Mortality rate in TBI patients is estimated to approximately 5 cases /100 000 persons and with a gender distribution of an average of 70% men (Masson et al. 2001). Mortality in severe TBI has gradually decreased over the years. In 1984 the mortality was equal to 39% and in 1996 it has decreased to 27% according to an american epidemiological study (Lu et al. 2005). The incidence of SAH has been stable during the last decades with approximately 10 cases /100 000 /year and with a gender distribution of an average of 66% women (Linn et al. 1996). Global mortality rate in SAH ranges from 32 – 67%. About 20% of SAH patients die before they reach hospital facilities (Ferro, Canhão and Peralta 2008).

Treatment that benefits outcome is of great concern though these cerebral emergencies mostly affect young and middle-age adults, with devastating social and financial consequences. Severe TBI and SAH cause personal tragedies in many ways and are associated with long-term disability and rehabilitation. There are considerable costs to society as a result of the severe cerebral emergency (Tagliaferri et al. 2006). The outcome after severe TBI is also related to the economics of society, as it is based on a society’s standard of care (Mauritz et al. 2008).

The overall principles for treatment of severe cerebral emergencies are to prevent and to treat the expansion of brain oedema and to maintain cerebral blood flow (CBF) for an adequate oxygenation to the brain in order to avoid development of secondary brain injuries.

An adequate CBF and preserved blood brain barrier (BBB) in the central nervous system (CNS) are the main conditions for sufficient oxygenation and metabolism. Due to trauma or vascular disease, an emergency to the brain parenchyma occurs. This can lead to damages of the BBB with increased permeability and development of brain oedema, as a secondary injury. Another secondary injury is
cerebral ischemia, which will arise whenever deliveries of oxygen and substrates to the brain fall below metabolic needs. That will lead to risks of development of endothelial dysfunction, inflammatory response, insufficient oxygenation and eventually cell deaths can occur (Albayrak et al. 1997, Holmin and Mathiesen 1995, Holmin et al. 1995).

Our treatment is focused on pathophysiological conditions caused by the emergency. The treatment uses physiological principles to maintain adequate CBF and to prevent brain oedema formation. Mandatory for the treatment is a tight cooperation between neurointensive care and neurosurgery (Grände, Asgeirsson and Nordström 2002, Naredi et al. 1998, Asgeirsson, Grände and Nordström 1994).

Many factors are involved in the care of the injured patient that can lead to the development of secondary cerebral injuries during initial resuscitation, transport, surgery and subsequent intensive care. A well functioning Intensive Care Unit (ICU) and a protocol driven therapy constitutes an important organizational frame for the detection, prevention and treatment of secondary brain injuries, after SAH and severe TBI, and is associated with improved results (Fakhry et al. 2004, Persson and Enblad 1999, Elf, Nilsson and Enblad 2002, Wahlström et al. 2005, Eker et al. 1998).
The Living organism is “a machine which of necessity functions in accordance with the physico-chemical laws of its individual components”

Claude Bernard, Paris 1865
“Introduction à l’étude de la médecine experimentale”

BACKGROUND

Basic Brain Physiology & Pathophysiology

The skull is composed of several bones fitted tightly together and creates a rigid space, from about the age of six - seven years in humans. The contents consist of brain parenchyma about 85% (1300-1400mL), cerebrospinal fluid (CSF) 5-10% (~ 125 mL) and intravascular blood volume (CBV) 5-10% (75-100 mL).

The cerebral circulation takes place within this closed space (the skull) with only a limited capacity to buffer variations in blood volume. Modification in vessel calibre (either passive or induced by cerebrovascular regulatory mechanisms) can lead to changes in CBV. A major function of CSF is to cushion the brain within the solid vault.

In normal conditions the total volume of brain parenchyma, CSF and CBV, is constant within the skull. There are compensatory mechanisms that care for certain expansion of one volume to keep the relationship of total volume constant. This endogenous compensational machinery will decrease the CSF by resorption and/or the blood volume by vasoconstriction, to keep the total volume constant.

In pathological conditions during the initial phase when there are compensatory mechanisms, an increase in one volume causes a decrease in any of the remaining volumes. If the pathological conditions progress, the unknown volume (Vx) will disturb the balance of the other three, and the compensatory mechanisms become exhausted. Increased volumes within the skull will lead to an increase in the intracranial pressure (ICP) (Smith 2008).

The equation, Monroe-Kellie principle, states that the sum of volumes (V) of the included substances is constant.

Monroe-Kellie;

\[ V_{cranium} = V_{brain~parenchyma} + V_{CSF} + V_{intravascular~blood} + (V_x); \ V_{cranium} \approx ICP \]

In severe TBI, a volume increase (Vx) occurs suddenly due to contusion or haemorrhage, the compensatory mechanisms hinder the increase of ICP from the beginning. During further pathological processes the mechanisms of compensation are brought to an end, the ICP will increase drastically (Shapiro 1975). This elevation of ICP is due to the small volume increase, which results in a large pressure elevation due to the rigid space of the cranium.
The relationship between intracranial volume and the ICP is described by the non-linear pressure-volume curve that consists of the three phases. The initial compensatory phase under normal conditions indicates that small variations of volume do not affect the ICP. The second phase has exhausted compensatory mechanisms due to pathological volumes. The third phase has no compensatory mechanisms left and a small volume increase makes a large impact and the ICP rapidly increases exponentially, as shown in figure 1. As a result of the elevated ICP forces the brain progresses to herniation (Steiner and Andrews 2006).

**Figure 1.** Pressure – volume curve.  
ICP = Intracranial pressure; $V$ = Volume

ICP is considered to be about 5 -12 mmHg under normal conditions in adults. In children, fontanelle and sutures can compensate for elevation in ICP until the age of six to seven years, if the process of volume changes in the skull is slow. Pediatric ICP might be age dependent and as low as two to four mmHg (Jones et al. 2003). In spite of the fact that the ICP might be lower in children, the threshold for treatment in severe TBI is proposed to be 20 mmHg in adults and children, above which outcome will be affected negatively (Marmarou 1991, Carney et al. 2003). The threshold for ICP in adults have became generally accepted but not yet fully validated. There have been some suggestions that lower ICP values for younger children may be used, although there are yet little data to support this (Chambers et al. 2006). The cerebral perfusion pressure (CPP) is a calculated value. CPP is the difference of the mean arterial pressure (MAP) minus the ICP (MAP - ICP = CPP). The CPP threshold levels are also supposed to be age-related but not yet validated. CPP threshold in children is accepted above 40 mmHg and in adults above 50 mmHg (Grände, 2006).

Autoregulation is the normal endogenous mechanism to control the cerebral circulation. The cerebral circulation is regulated by changes of vascular resistance, to keep CBF constant during variations of the systemic blood pressure. CBF is
Background

largely independent of perfusion pressure when autoregulation is intact. The autoregulation is functioning within the limits for (MAP) between 50 mmHg to 150 mmHg. Systemic blood pressure with extremes beyond these limits makes the CBF become linear to the systemic pressure (Wahl and Schilling 1993). Severe TBI patients might have a general or a local disturbance in autoregulation and the CBF tends to be dependent on the systemic blood pressure in those areas. Loss of autoregulation makes direct differences with elevated CBF, CBV and ICP, with risk of deterioration for the patient (Rangel-Castilla et al. 2008). The loss of autoregulation will therefore lead to that high systemic blood pressure will increase capillary hydrostatic pressure and thereby increase the risk of fluid filtration over the capillary membrane and then development of brain oedema.

The cerebral vascular resistance can be modulated by local-chemical and endothelial factors, and by the release of transmitters from perivascular nerves. Endothelial factors such as endothelium derived constrictor and relaxing factors, nitric oxide (NO) and prostacyclin (PGI₂), can be released by physical stimuli such as shear stress, haemorrhage, neurotransmitters, and cytokines. Histamine, bradykinin, interleukins and free radicals influence cerebrovascular resistance, dilating capacitance vessels and increasing the permeability of the BBB under pathological conditions. These substances are released by trauma, ischemia, seizures and/or inflammation. Cerebral arteries are innervated by sympathetic and parasympathetic systems. The sympathetic-noradrenergic fibres originate from the superior cervical ganglion and release constricting transmitters such as norepinephrine (Wahl et al. 1993, Wahl and Schilling 1993).

The brain has high metabolic demands and is dependent on continuous delivery of oxygen and glucose and elimination of carbon dioxide. The delivery of oxygen is dependent on adequate CBF. In the healthy brain parenchyma, the need for oxygen and glucose is intimately connected to the regulation of CBF. Under circumstances with elevated activity of the CNS the consumption of oxygen and glucose increase parallel to the increase of CBF. Under conditions with damaged brain parenchyma there may be anaerobic metabolism under shorter periods (Robertson and Cormio 1995). Elevated ICP hinders an adequate CBF and the metabolic supply to the cells is impaired. This leads to cell ischemia with an oedema development.
"Mollycewels is a stickin’ together of millions of atoms o’ sodium, carbon, potassium o’ iodide, etcetera, that, accordin’ to the way they’re mixed, make a flower, a fish, a star that you see shinin’ in the sky, or a man with a big brain like me, or a man with a little brain like you!"

Brian Cathcart
“The fly in the cathedral”

**Background**

The endothelium is the inside layer of the entire vascular system, created by a monolayer of endothelial cells and their intracellular junctions. It separates the intravascular (blood) fluid from the vascular smooth muscle cells and the interstitial compartment. The endothelial cell has multiple functions and is considered to be an endocrine organ with the ability to release different substances, for example prostacyclin (PGI$_2$), nitric oxide (NO) and asymmetric dimethylarginine (ADMA) (Davies and Hagen 1993).

The cerebral vascular system has a specific constitution of the endothelial cells with tight junctions, the so-called BBB, which keeps the fluid and the interstitium of brain parenchyma separated. The exchange of substrates between blood and tissue take place mainly across the capillary endothelium. These endothelial cells are welded tightly together and do not allow for the free flux of substances or fluids except water, and permit the passage of sodium and chloride ions. It regulates the relationship of molecules and cells between the circulation and the CNS. The cerebral capillary endothelium is impermeable to large or polar molecules but highly permeable to most lipid soluble substances (Staddon and Rubin 1996). The hydrostatic pressure due to blood pressure, the osmotic pressure due to solubles (salts and colloids) and the active transportation pumps or passive transportation by vesicles are components that also affect changes over the BBB (Wahl et al. 1993). The transcapillary hydrostatic pressure and the oncotic plasma pressure is equally large, about 20-25 mmHg. The crystalloid osmotic pressure is a result of the balance of the capillary intravascular space, the interstitial space and the intracellular space. This balance of forces, at a steady state, results in no net fluid exchange between spaces (Grände et al. 2002).

**Endothelial dysfunction**

After trauma or haemorrhage the cerebral vascular endothelium alters its regulatory functions, and the consequences can be abnormal cell functions. Endothelial dysfunction can be defined as an imbalance between vasodilatation and vasoconstriction, pro- and anticoagulation and/or between inhibiting and promoting inflammation (De Meyer and Herman 1997). The activation of the inflammatory cascade due to injury has a considerable role in initiating endothelial cell
proliferation of the vascular wall. There are factors that can indicate endothelial dysfunction and serve as potential biomarkers (Table 1) (Unterberg et al. 1991, Münzel et al. 2008). Endothelial dysfunction is partly dependent on low levels of vascular NO. Free radicals are produced in the endothelial cells under both normal and pathological conditions. The capacity for neighbouring endothelial cells to repair an injury can be limited and vascular integrity impaired if the oxidative stress with increased free radical production is persistent (Deanfield, Halcox and Rabelink 2007).

The inflammatory cascade of the endothelium induces the production of the pro-inflammatory markers. Certain pro-inflammatory interleukins (IL) stimulate the production of C-reactive protein (CRP) and fibrinogen in hepatocytes (Zhang 2008). The cytokines are versatile proteins with the purpose of controlling leukocyte activity.

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Marker</th>
<th>Signal/Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory cascade</td>
<td>Interleukins</td>
<td>Regulate leukocyte activity</td>
</tr>
<tr>
<td>Inflammatory cascade</td>
<td>CRP, fibrinogen</td>
<td>Inflammatory reaction</td>
</tr>
<tr>
<td>Inflammatory cascade</td>
<td>sICAM-1</td>
<td>Reflects the extent of endothelial cell activation and damage</td>
</tr>
<tr>
<td>L-arginine / NO pathway</td>
<td>ADMA</td>
<td>Impairs NO production, eNOS uncoupling</td>
</tr>
<tr>
<td>Oxidation processes</td>
<td>ADMA</td>
<td>Inactivates NO, Oxidative stress</td>
</tr>
</tbody>
</table>

Table 1. Markers for pro-inflammation and endothelial dysfunction.

CRP = C-reactive protein; sICAM = Soluble intracellular adhesion molecule; NO = Nitric oxide; ADMA = Asymmetric dimethylarginine; NOS = Nitric oxide synthase

Inflammation

Inflammation is a complex of sequential alterations as a reaction to damaged tissue. It is a “military” action in protection, to combat different events or agents that assault the body.

Trauma, bacteria, burns and chemical exposures damage the tissue and cause immediate inflammatory reactions, either locally and/or systemically. The damaged tissue liberates substances that can cause increased permeability of the capillaries and vasodilatation. This occurs with large quantities of proteins and fluid leakage into the interstitium and leads to the formation of oedema. Both histamine and bradykinin from the damaged area can affect permeability in the cerebral capillaries (Unterberg et al. 1991, Möller and Grände 1997)
The damaged tissue also stimulates the immune system, the cellular and/or the humoral immune response which partly cover each other. The cellular immune defence stimulates cells (macrophages, granulocytes, T-and B-lymphocytes, microglia cells in CNS) to act against intracellular microorganisms such as bacteria, viruses and fungi. The humoral immune response stimulates the production of cytokines and the cascade of complement activation, and uses antibodies in defence of infections. Cytokines are small proteins, some named interleukins, and are used as signal molecules between cells in the pro-inflammatory period (Morganti-Kossmann et al. 2007).

The secretion of pro-inflammatory mediators can result in aggravated inflammation, with leukocyte adhesion to the vascular endothelium and platelet aggregation. Consequences to this can be microvascular obstruction, microvascular injury, endothelial dysfunction, vasodilatation, increased vascular permeability and this can lead to interstitial oedema (Martin et al. 1997). The interaction of activated endothelium and leucocytes results in loss of integrity of microcirculation and decreased perfusion, which in turn aggravates the inflammatory system through the release of reactive oxygen radicals and cytokines (Botha et al. 1995, Maier and Bulger 1996). Clinical and experimental studies in trauma show that increased cytokine production is associated with systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), multi-organ dysfunction syndrome (MODS) and that can influence outcome (Stahel et al. 2000, Winter et al. 2004, Guirao and Lowry 1996).

The interleukin-6 (IL-6) levels correlate with the degree of inflammation and severity of injury. IL-6 is the most important mediator of acute-phase protein synthesis and promotes inflammation by up-regulation of sICAM-1 and chemotaxis (Pape et al. 2007, Singhal et al. 2002, Miñambres et al. 2003). Serum levels of IL-6 have been shown to correlate with the incidence of MODS, ARDS, and outcome after trauma (Napolitano et al. 2000). This interleukin seems to play a double role in the inflammatory reaction, involved in both the defence and the repair mechanisms that follow trauma (Lenz, Franklin and Cheadle 2007). A difference was shown between the systemic response and the central nervous system response to IL-6 after severe TBI. Elevated levels of IL-6 in CSF was associated with a favourable prognosis, while increased IL-6 levels in serum was associated with poor outcome in patients (Winter et al. 2002, Singhal et al. 2002, Miñambres et al. 2003).

The interleukin-8 (IL-8) is the most potent endogenous chemotactic cytokine and chemoattractant for leucocytes to the site of inflammation (Singhal et al. 2002, Morganti-Kossmann et al. 2007). IL-8 is produced by a large variety of cells including macrophages/monocytes. The production starts early after trauma and persists a long time, even weeks Elevated IL-8 concentrations in serum are an expression of inflammation and not an expression of endothelial reactions (Lenz et al. 2007).
The soluble intracellular adhesion molecule (sICAM-1) have increased levels in serum as a result from damage to the endothelium secondary to systemic inflammatory processes, and are related to the development of organ failure. It forms a connection between leucocytes and endothelium expressed by the neutrophil activation and is necessary for adequate transmigration of leucocytes through the endothelium (Otto et al. 2000, Feuerstein, Wang and Barone 1998, Parkos 1997).

CRP is a non-specific marker for inflammation, and is normally elevated within 48 hours after trauma (Giannoudis 2003). The hepatic synthesis of CRP is induced by IL-6, and the degree of systemic inflammatory response is correlated to the level of IL-6 (Pape et al. 2007, Zhang 2008). CRP is relatively non-specific and not entirely associated with the degree of post-traumatic complications (Du Clos 2000). CRP can mediate an increase sICAM-1 expression and reduce a NO production, and thereby cause a pro-inflammatory and a pro-thrombotic environment (Münzel et al. 2008)

**Asymmetric Dimethylarginine (ADMA)**

In Lancet 1992, Vallance and Leone described for the first time that endothelial nitric oxide synthase (NOS) could be competitively inhibited by an endogenous compound, ADMA which could inhibit the production of NO (Vallance et al. 1992)(Figure 2). NO is developed from L-arginine by NOS. NO is a common mediator of vascular tone, host defence reactions and neurotransmissions (Moncada, Palmer and Higgs 1991).

ADMA evolves from proteolysis of L-arginine from cells in apoptosis or in necrosis. Elevated plasma concentrations of ADMA represent a risk factor for the development of endothelial dysfunction. The elevation of ADMA concentrations in plasma leads to impaired endothelium-dependent vasodilation and increased leucocytes and platelets adhesions (Böger 2003, Siekmeier, Grammer and März 2008). There are reports that ADMA in CSF is increased during the first week after SAH and is correlated with development of cerebral vasospasm (Pluta et al. 2005b, Pluta et al. 2005a, Pluta 2006, Jung et al. 2004, Martens-Lobenhoffer et al. 2007).

It is unknown whether elevated ADMA plasma concentrations may be considered simply as a marker for cardiovascular disease or whether increased ADMA levels per se may predispose the development of vascular diseases (Sydow and Münzel 2003, McCarty 2004) Increased levels of ADMA have been established in patients with stroke, hypertension, renal insufficiency, diabetes mellitus, hypercholesterolemia, pre-eclampsia, critically ill patients and smokers (Wanby et al. 2006, Zoccali et al. 2002, Savvidou et al. 2003, Nijveldt et al. 2003b, Nijveldt et al. 2003a, Siroen et al. 2006). Thus, in all conditions where vascular oxidative stress is enhanced there are elevated ADMA concentrations. Increased oxygen-derived free radicals are linked to endothelial dysfunction and oxidative stress has been shown to elevate the ADMA concentrations. The vascular tone and the thickness of the
Background

Intimal layer in damaged vessels is directly proportional to endothelial dysfunction and ADMA levels (Sydow and Münzel 2003, Kielstein et al. 2006, Cooke 2000).

![Diagram of ADMA effect on NOS]

**Figure 2.** The ADMA effect on NOS. ADMA = Asymmetric Dimethylarginine; NOS = Nitric oxide synthase

Brain Oedema

There are physiological forces that regulate fluid fluxes across the damaged BBB. Various types of brain oedema are complications of CNS emergencies and can develop over the course of time in the brain due to illness, trauma and/or treatment. There are theoretically different forms of oedema and they can appear together or alone, although they are probably due to separate causes and pathogenesises (Milhorat 1992) (Table 2).

Cytotoxic oedema is cellular damage due to ischemic events and can occur in some degree of focal lesions (Siesjö 1988). Hydrostatic oedema develops after malignant hypertension or as a result of acute hydrocephalus. Vasogenic oedema due to a disruption of BBB in focal lesions can increase gradually and cause a mass effect and thereby increase ICP.

Contusions have typical vasogenic oedema which develops progressively with a maximum several days after trauma (Betz, Iannotti and Hoff 1989, Holmin and Mathiesen 1995). The trauma itself causes interstitial oedema by destruction of the regulating machinery of the BBB and by vasoactive substances that are released from cascade systems. The cascades are activated by damaged neurons, haematomas, contusions and inflammation. This in turn will cause increased capillary permeability and fluid fluxes into the interstitium (Holmin and Mathiesen 1995, Holmin et al. 1995, Wahl et al. 1993).

The undamaged brain is protected from volume changes that follow variations in capillary hydrostatic pressure and oncotic pressure. In the damaged brain with
increased permeability the transcapillary hydrostatic pressure can be out of balance with the transcapillary oncotic pressure. Thereby the filtration of water across the capillary membrane might not be halted by the otherwise opposing oncotic gradient, and an oedema formation can develop. Decreased hydrostatic capillary pressure in combination with preservation of normal colloid osmotic pressure induces theoretically transcapillary fluid absorption. Increased systemic arterial pressure as a result of other factors causes increased hydrostatic pressure, which then can result in fluid filtration and progression of oedema (Asgeirsson and Grände 1994, Grände, Asgeirsson and Nordström 1997, Contant et al. 2001, Robertson 2001).

<table>
<thead>
<tr>
<th>Type</th>
<th>Cause</th>
<th>Pathogenesis</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxic</td>
<td>Anoxia, Ischemia</td>
<td>Cell metabolism derangement</td>
<td>Intracellular</td>
</tr>
<tr>
<td>Hydrostatic</td>
<td>Hypertension, Hydrocephalus</td>
<td>Hydrostatic gradient</td>
<td>Interstitial</td>
</tr>
<tr>
<td>Vasogenic</td>
<td>Focal lesion, Inflammation</td>
<td>Blood brain barrier disturbance or collapse</td>
<td>Interstitial</td>
</tr>
</tbody>
</table>

Table 2. Different types of brain oedema.

The development of brain oedema due to increased hydrostatic pressure can be physiologically explained by the two-pore theory. The two-pore theory for transcapillary exchange of fluids and substances describes the exchange. This exchange occurs mainly through small and large pores. The exchange is mainly passive through the pores in the tight junctions of the capillary membrane. The larger pores are less common and placed mainly on the capillary venous side. Proteins are passively exchanged by convection through the larger pores. This theory describes the importance of transcapillary hydrostatic pressure since there is a continuous fluid filtration. The colloid osmotic pressures are about equal on each side of the membrane, therefore the osmotic forces in normal situation is negligible. Increased forces of the hydrostatic pressure will lead to increased fluid filtration and thereby increased protein transfer through the large pores. In pathological conditions with an increase in capillary permeability and an increase of large pores, the hydrostatic pressure will increase both the fluid and the protein extravascular losses (Rippe and Haraldsson 1994).

Severe traumatic brain injury

The classification of severe TBI involves a heterogeneous assembly of injuries. The definition of severe TBI can be based on the pathology and physiology of vascular and/or parenchymal injury, or on the degree of consciousness. Epidural, subdural and intracerebral haematomas and traumatic subarachnoid haemorrhage are vascular injuries in different anatomical sites. Contusions, lacerations and diffuse
Background

Axonal injury belong to parenchymal damages with different pathology. The degree of severity is based on the pathophysiological condition and the amount of damaged parenchyma or amount of haematoma. The severity can also be judged by the degree of loss of consciousness. From the emergency physician's standpoint, patients with severe TBI are those that present with a Glasgow Coma Scale (GCS) score less than 9 (Zink 2001).

Primary Brain Injury

The brain is the most, well-protected organ in the body as it is placed inside the hard shell of the skull bone, with shock absorbers of CSF and the scalp. A forceful blunt trauma against the head or a violent fall makes the brain accelerate and decelerate or rotate. The delivery of a blow to the head represents a transfer of energy, part of which manifests itself as a short-lived pressure change within the skull (Orfeo et al. 1994). These mechanical forces of tensile stress or shear stress result in damage to the CNS, brain parenchyma and/or parts of the vascular system. Tensile stress is due to pull- and compression forces which create contusions. Shear stress is due to rotation and causes damage in the white matter which may result in diffuse axonal injury. Lacerations are often due to penetrating trauma and various haematomas appear as a result of the injured vessels. The primary injury appears directly upon the impact of trauma where parts of CNS becomes destroyed and damaged permanently (Miller and JD 1978).

Secondary Brain Injury

The area around the primary brain injury in the parenchyma is called the penumbra. It is vulnerable to impaired cerebral circulation. When the area is exposed to hypoxia, hypotension, hyperventilation, hypercapnia, hyperthermia, inflammatory reactions and/or a impaired metabolism, it can lead to a secondary brain injury (Feuerstein, Liu and Barone 1994, Muizelaar et al. 1991, Diaz-Parejo et al. 2003). These events are avoidable factors but they can also lead to oedema formation and ischemia, and result in an elevation of ICP. This secondary brain injury is a complication of the primary brain injury, but has a potential of recovery with active and preventive treatment. Patients with severe TBI and exposure to events of hypoxia and/or hypotension are related to have a higher incidence of morbidity and mortality (Chesnut and RM 1993, Chesnut 1995, Chesnut 1998, Pigula et al. 1993, Marmarou 1991, Winchell, Simons and Hoyt 1996, Stocchetti, Furlan and Volta 1996)

Management of severe TBI patients

A CPP management is an accepted therapy in parts of the world. It is based on the principle to increase the level of CPP by increased systemic blood pressure and thereby increase the CBF. This is a management without considering the effects on ICP levels. Increase in CBF results in an increase of CBV and thereby even an increase in ICP. American Guidelines from the Brain Trauma Foundation 1995
advocated a CPP management with limits above 70 mmHg. The American guidelines from 2007 have lower limits of CPP and the recommendation is now a CPP above 60 mmHg (Bullock et al. 1996, Bullock, Chestnut and al. 2000, Bullock and Povlishock 2007, Rosner, Rosner and Johnson 1995, White and Venkatesh 2008).

The ICP-targeted therapy

The ICP-targeted therapy in this thesis, involves the close combination of offensive intensive care and active neurosurgery to control intracranial volume by physiological principles modified from the “Lund-concept” protocol (Asgeirsson et al. 1994, Eker et al. 1998, Wahlström et al. 2005) The overall aim of the ICP targeted therapy is to control brain volume and cerebral perfusion and thus maintain a steady ICP ≤ 20mmHg. The approach to control ICP levels is to aggressively treat space-occupying lesions with neurosurgery, to reduce stress response and cerebral metabolism through continuous sedation, to reduce capillary hydrostatic pressure with intravenously administered α-agonist and β₁-antagonist, to prevent oedema formation by maintenance of colloid osmotic pressure and normovolemia, and to reduce the cerebral blood volume if needed (Grände 2006) (Table 3).

<table>
<thead>
<tr>
<th>Standard basic treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurosurgery</strong></td>
</tr>
<tr>
<td>ICP monitoring device</td>
</tr>
<tr>
<td><strong>Normotension</strong></td>
</tr>
<tr>
<td>ICP &lt; 20mmHg, CPP &gt; 50mmHg / Children CPP &gt; 40mmHg</td>
</tr>
<tr>
<td><strong>Normoventilation</strong></td>
</tr>
<tr>
<td>PaO₂ ≥ 12kPa, PaCO₂ 4.5 – 5.5kPa</td>
</tr>
<tr>
<td><strong>Normovolemia</strong></td>
</tr>
<tr>
<td>Hb ≥ 110g/L, Albumin ≥ 40g/L</td>
</tr>
<tr>
<td><strong>Normal serum sodium</strong></td>
</tr>
<tr>
<td><strong>Normo-glycaemia</strong></td>
</tr>
<tr>
<td><strong>Normothermia</strong></td>
</tr>
<tr>
<td><strong>Continuous sedation</strong></td>
</tr>
<tr>
<td><strong>Continuous analgesia</strong></td>
</tr>
<tr>
<td><strong>Nutrition</strong></td>
</tr>
</tbody>
</table>

Table 3. Standard basic treatment

1. **Neurosurgery**

is performed as soon there is need of removing space-occupying lesions after blunt trauma. The evacuation of haematoma and/or contusions is in order to reduce intracranial content and thereby ICP. ICP monitoring is mandatory either by the use of an intraparenchymal sensor (Camino 1993-1996 or Codman MicroSensor™)
Background

from 1996; Johnson & Johnson Professional Inc. Raynham, MA, USA) and/or by a ventriculostomy. The intraventricular catheter is used intermittently for drainage of CSF and thereby decreases ICP (Grände 2006). The zero-pressure baseline for the ventriculostomy is set at the preauricular level with the patient in a supine position. In life-threatening situations the use of decompressive craniectomy can significantly reduce high ICP levels (Polin et al. 1997, Olivecrona et al. 2007).

2. Normotension

is defined in accordance to age for systemic arterial pressure, ICP and CPP. MAP is kept within normal limits, an average of 65 – 100 mmHg for adults. Systemic blood pressure is invasively measured with the zero-pressure baseline set at the heart level.

Hypotension, in adults (< 90 mmHg systolic pressure) and children (systolic pressure < 70 mmHg + 2 x age), is aggressively treated primarily by volume trans-fusions. Vasoactive drugs are avoided but used before normovolemia can be reached.

Head trauma can provide impaired autoregulation and followed by that the CBF will depend on CPP. During pathophysiological conditions the treatment should not cause the CPP to become lower than 50 mmHg in adults and not lower than 40 mmHg in children (Bullock et al. 2000, Carney et al. 2003).

After establishment of normovolemia with colloids, a combined increase of ICP and CPP is treated by a combination of metoprolol (max 0.3 mg/kg/24h) and clonidine (max 0.8 µg/kg/24 h) to normalise systemic blood pressure and reduce sympathetically mediated stress with little effect on the cerebral circulation. The capillary hydrostatic pressure is reduced without any substantial cerebral vasodilatation (Asgeirsson et al. 1994, Grände 2006).

Metoprolol is a β1-antagonist with anti-hypertensive and heart rate reducing effects. Theoretically, the TBI patients that are treated with metoprolol could acquire an effect on the sympathetic nervous system with reduced catecholamine reaction, which could have protective consequences on the heart and the lungs and have beneficial effects on outcome (Cotton et al. 2007, Riordan et al. 2007, Inaba et al. 2008).

Clonidine is a α2-agonist which acts on cardiovascular control receptors in the medulla oblongata and inhibits sympathetic outflow, which results in stress reducing, decreased cardiac output and heart rate (Maze and Tranquilli 1991, Payen et al. 1990).

3. Normoventilation

with PaCO2 4.5–5.5 kPa, PaO2 >12 kPa and positive end expiratory pressure (PEEP) 4–8 cm H2O to avoid atelectasis. The patient is always intubated and mechanically ventilated as a standard procedure.
Hyperventilation is not an option in the protocol but can be used when an emergency situation occurs with symptoms of herniation (Muizelaar et al. 1991).

4. Normovolemia;
   To ensure and maintain normovolemia and normal colloid osmotic pressure in combination with adequate cerebral oxygenation, transfusions of hyperoncotic albumin 20%, albumin 4%, and erythrocytes are used. Replacement of the patient’s intravascular volume (preload) is required for adequate oxygen delivery and for optimal hemodynamic stability and the systemic blood pressure (after load) is necessary to avoid secondary injuries developing due to hypotension and hypoxia (Asgeirsson et al. 1994, Grände 2006, Clifton et al. 2002). There is no randomised controlled trial or golden standard for evaluating normovolemia in patients (Heier et al. 2006).

   Hypovolemia is clinically considered in patients with combinations of tachycardia, low diuresis, low albumin and/or anaemia and low central venous pressure (CVP)(Madjdpour, Heindl and Spahn 2006). Normovolemia is considered clinically achieved by heart rate less than 100 beats/min, adequate diuresis more than 0.5 ml/kg/hour in adults, acceptable peripheral circulation (warm hands and feet), an average CVP 8-10 mmHg, albumin above 35 g/L and Hb more than 110 g/L.

*Albumin*

According to the ICP-targeted therapy, albumin is kept within the normal limits. Albumin is an intravascular and extravascular protein. Albumin is of vital importance in maintaining the colloid oncotic pressure and thereby keeping the intravascular volume constant. Albumin administration include volume expansion and hemodilution, increased albumin concentration in serum, and colloid osmotic pressure (Evans 2002, Ernest, Belzberg and Dodek 1999) Albumin is an important carrier of free fatty acids, which white blood cells need as energy substrate in combating infections. Albumin is responsible for 75-80% of osmotic pressure and is water soluble. Albumin has negative charges around the protein molecule which attract sodium, thus holding water (Quinlan, Martin and Evans 2005).

Decreased levels of plasma albumin and thereby decreased colloid oncotic pressure were associated with increased oedema formation in experimental studies. The administration of hyperoncotic albumin decreased brain oedema development (Belayev et al. 1998). Hemodynamic stability was shown in studies with albumin and slightly negative fluid balance by furosemide, which resulted in significantly improved oxygenation in patients and lowered the ICP in severe TBI in animals (Albright, Latchaw and Robinson 1984, Martin et al. 2005).

Hyperoncotic albumin has an anti-inflammatory effect in acute respiratory failure experimental settings, and reduces microvascular permeability as well as inhibiting endothelial cell apoptosis. The hyperoncotic albumin effect modulates neutrophil adhesion and activation in an anti-inflammatory behaviour (Powers et
al. 2003). Albumin has also an ability to modulate capillary permeability (Quinlan et al. 2005).

Haemoglobin

The main reasons behind giving erythrocyte transfusions are for volume resuscitation and to achieve optimal oxygen delivery to tissues. The erythrocytes stay in the vascular space for a long-lasting period of time, and are consequently exceptional volume expanders (Henry and Scalea 1999).

The amount of oxygen delivered is quantified by the product of cardiac output and the arterial oxygen content. The relation between oxygen delivery and oxygen consumption due to requirements is more than 2:1 under normal conditions. This relation changes when haemoglobin reduces below critical concentrations, which then creates deceased oxygen delivery and which can affect oxygen consumption. As soon as oxygen delivery is lower than oxygen consumption there will be a progression of ischemic conditions (Madjdpour et al. 2006).

The main energy source for the brain is a continuous delivery of metabolic substrates of oxygen and glucose. The cerebral metabolism is nearly totally aerobic, and corresponds to about 20 - 25% of the total body oxygen consumption.

Erythrocyte transfusions can increase cerebral oxygenation in patients with severe TBI and SAH. Two studies show that an increase in brain tissue partial pressure of oxygenation (PtiO₂) can be reached when erythrocytes are transfused to hemodynamically stable patients. A PtiO₂ < 12 mmHg in the brain is considered hypoxic. Patients with low levels of PtiO₂ were transfused with erythrocytes and reached normal PtiO₂ levels. The normal levels were preserved for an average of 24 hours (Leal-Noval et al. 2006, Smith et al. 2005). CPP does not increase brain oxygenation per se (Sahuquillo et al. 2000). In experimental settings, the combination of TBI and anaemia cause increased injury to the brain parenchyma and impaired cerebral autoregulation (DeWitt et al. 1992).

Transfusion can lead to infectious diseases, transfusion reactions, and immune suppression (Chang et al. 2000, Silliman et al. 2003, Deitch and Goodman 1999). There are suggestions that immunosuppressive effects and activation of the inflammatory cascade systems including the response of blood transfusions may be responsible for septic morbidity associated with multi-organ failure (Deitch and Goodman 1999).

5. Normal serum sodium

Serum sodium is actively maintained within normal limits (135-150 mmol/L). Serum sodium levels are controlled several times per day.

6. Normoglycaemia

To ensure normoglycemia, controls are provided several times per day. Treatment request with short-acting insulin is according to normal glucose limits (3-8 mmol/L).
7. Normothermia
Hyperthermia (>38° C) is treated by paracetamol and/or by surface cooling.

8. Sedation and analgesia
Continuous sedation and analgesia with infusions of midazolam and fentanyl are performed to reduce stress-response and cerebral energy metabolism. Drug doses are adjusted to the patients comfort and in co-operation with ventilator modes. Midazolam is used for sedation and might have an anti-seizure effect that is not considered in the treatment protocol. Fentanyl is used for analgesia.

If ICP continuously stays above 20 mmHg, a continuous low-dose pentothal (0.5–3 mg/kg/hour) infusion is added. The dose is adjusted to a delta-wave pattern, and monitored continuously or intermittently with electroencephalography (EEG).

Low-dose of pentothal induces cerebral vasoconstriction in normal areas and reduce metabolic demands for oxygen. High-dose administration of pentothal can induce complicating effects such as hypotension, cerebral vasoparalysis, and depressive effect of the immune system (Schalén, Messeter and Nordström 1992, Nordström et al. 1988)

Awakening tests, muscle relaxants or prophylactic antiepileptic drugs are not options in the protocol and are not used.

9. Nutrition
The protocol recommends early enteral feeding with a low-energy of 15-20 kcal/kg/24 hours to adults. Nutritional treatment with glucose fluid infusion with electrolytes is used daily as a complement to enteral feeding.

Dihydroergotamine (DHE)
is a rarely used drug treatment in the treatment protocol, and used only in an intracranial hypertensive crisis. DHE induces a venous vasoconstriction and reduces ICP by decreasing intracranial blood volume. It causes precapillary vasoconstriction and lowers the capillary hydrostatic pressure. The starting dose is 0.6 – 0.8 µg/kg/h and is gradually reduced over a period of five days. DHE is discontinued if complications occur, such as compromised peripheral circulation (Asgeirsson et al. 1994).

Prostacyclin (epoprostenol)
Prostacyclin (PGI₂) is an endogenous prostaglandin produced in the endothelium of the vascular system (Moncada et al. 1976b) (Figure 3). Prostacyclin is added to the protocol to prevent brain oedema development, to recover microcirculation and thereby improve the treatment results.
Background

The main purpose of endogenous produced prostacyclin is to prevent aggregations and adhesions of leukocytes and platelets and thereby control interactions between the endothelium and the circulating blood and interact with the vascular resistance (Vane, Anggård and Botting 1990, Vane and Botting 1995b, Campbell et al. 1996) (Figure 4). Prostacyclin is the most potent endogenous inhibitor of platelet aggregation. It inhibits leukocyte activation and inhibits leukocyte adhesion (Moncada et al. 1976a, Moncada and Vane 1979a, Murata et al. 1997) (Vane and Botting 1995a, Higgs et al. 1978, Jones and Hurley 1984). The effect of prostacyclin is a dose-dependent vasodilation (Moncada et al. 1976c). It is described that prostacyclin has no importance for the control of the regulation of vascular tone during normal conditions. Instead, NO has a significant effect on basal vascular tone (Möller and Grände 1999b). Low prostacyclin concentrations elevates the risk of impaired microcirculation due to vasoconstriction, leukocyte adhesion and platelet aggregation. Prostacyclin has an effect on the inflammatory response, and has been shown to suppress TNF α and IL-1 produktion (Jörres et al. 1997, Crutchley, Conanan and Que 1994). Prostacyclin can even affect the microvascular permeability especially on the postcapillary venules (Möller and Grände 1999a).

Prostacyclin is produced from arachidonic acid, by the intersection from prostaglandin PG₂ to PH₂ and then a junction to either prostacyclin or tromboxane A₂. In pathophysiological conditions such as trauma, the equilibrium shifts towards increased tromboxane A₂ concentrations (Figure 3) (Gryglewski et al. 1978, Moncada and Amezcua 1979, Vane and Corin 2003). Normal concentrations of
Background

Prostacyclin suitable to endogenous production are 0.06 – 0.1 ng/kg/min (Scheeren and Radermacher 1997, Ritter, Orchard and Lewis 1982).

Vasoactive drugs

Vasoactive drugs are not a part of the ICP-targeted therapy used in this thesis, but are still used in order to maintain hemodynamic stability.

Norepinephrine is primarily a vasoconstrictor with mixed α- and β- agonist properties. The predominant α-1-adrenergic effect can produce intense arterial vasoconstriction, and acts in low doses as a β-agonist and thus even increases pulmonary vascular resistance.

Phenylephrine is a selective α-adrenergic agonist drug, and elevates blood pressure by increasing systemic vascular resistance via vasoconstriction. Reflex increase in parasympathetic tone results in a slowing of the pulse. The lack of β-adrenergic action provides a non-inotropic effect, and no cardiac acceleration, and no relaxation of bronchial smooth muscle. Cardiac output and renal blood flow may decrease (Guyton and Hall 2006).

Both norepinephrine and phenylephrine are considered to have no significant influence on cerebral hemodynamics in healthy volunteers. It is thought that the BBB prevents the vasoactive drugs from having a direct effect on the cerebrovas-
circular smooth muscle cells (Strebel et al. 1998). Phenylephrine was used in experimental settings of TBI to increase CPP. The studies showed no decrease in brain oedema, in brain tissue volume or in improved neurological outcome (Talmor et al. 1998, Rassler et al. 2003).

**Microdialysis**

Microdialysis technique uses a semi-permeable membrane through which substances flow due to passive diffusion. There is a concentration gradient, and substances diffuse from higher to lower concentration over the membrane, to reach equilibrium. The catheter has a double lumen where the dialysate is infused in the inner lumen and then at the end of the catheter is diffused in the space between inner lumen and the outer shell. The semi-permeable membrane is the outer shell. Passive diffusion from the interstitial space outside the semi-permeable membrane to the inside occurs at the end of the catheter (Chaurasia et al. 2007).

Four major factors influence the concentration of substances in the dialysate: (Ungerstedt 1991, Hutchinson et al. 2000).

1. Membrane length. The recovery of dialysate is proportional to the size of the dialysis membrane area. Thus a higher recovery is reached with a longer membrane in standardized size catheters.

2. Properties of the dialysis membrane. The size of the pores of the dialysis membrane defines the size of the substance that can diffuse through the membrane. Standard membrane pore cut is 20 kD, thus amino acids, ions and metabolites can pass through the membrane pores.

3. Flow rate of the perfusion fluid. The recovery for a given microdialysis catheter increases when perfusion rates are kept low. The relation between concentration in the dialysate and flow rate is exponential.

4. The diffusion coefficient. It is specific for each substance due to its molecular weight. High molecular weight corresponds to a low diffusion coefficient (Ståhl et al. 2001).

**Cerebral glucose, lactate and pyruvate**

Glucose is the sole substrate for cerebral energy metabolism under normal aerobic conditions. It is actively transported across the BBB, and under normal conditions there is rapid transportation between extra and intracellular compartments. The main amount of glucose is intracellularly oxidized to pyruvate and then to CO₂ and H₂O in the citric acid cycle.

The anaerobic pathway of glucose metabolism yields lactate production, thus the pyruvate is reduced to lactate due to a shortage of oxygen. Intracellular glucose concentrations decrease rapidly if the blood supply is insufficient in relation to metabolic demands, as in ischemic situations.
The lactate/pyruvate (L/P) ratio is considered to be a reliable marker for the redox state of the brain. The redox state is the amount of the relative shortage of oxygen supply in relation to demand. Lactate and pyruvate are diffusible through cell membranes and thus the L/P ratio in the tissue should reflect the changes of the redox state (Siesjö 1978).

Subarachnoidal Haemorrhage (SAH)

SAH is an emergency with an acute rupture of an intracerebral arterial aneurysm. SAH represents about 5% of all strokes, and is more common in females. Secondary insults such as cerebral haemorrhages, vasospasm and ischemia are the main causes of damages after SAH. Deaths due to SAH are caused by sudden cardiac arrhythmias, global cerebral ischemia, or brain oedema (Brisman, Eskridge and Newell 2006, Ferro et al. 2008, van Gijn and Rinkel 2001). Release of massive quantities of catecholamines lead to cardio-respiratory complications and hydrostatic pressure effects on capillaries occur prior to general medical complications (Macmillan, Grant and Andrews 2002, Naredi et al. 2006, Naredi et al. 2000). Following acute SAH there is an activation of platelet aggregation and an increase in the release of thromboxane A₂ by α- and β-stimulation (Ohkuma et al. 1991). Extravasation of blood is followed by hemolysis and deposition of heme-containing compounds. This is supposed to initiate a sequence of redox reactions and generating various free radical species. Thus, the acute SAH induces an inflammatory reaction cascade with risk of developing endothelial dysfunction.

Scoring / Appendix

See appendix pages 59 – 64.
Figure 5. The ICP-targeted therapy algorithm.
ICP = Intracranial pressure; EEG = Electroencephalogram
Aims of the thesis

AIMS OF THE THESIS

• To evaluate outcome in patients with severe TBI treated with an ICP targeted therapy focused on physiological principles for cerebral volume regulation and preserved microcirculation (papers I + II + III + IV)

• To evaluate the implementation of the ICP-targeted therapy in paediatric patients with severe TBI (paper I)

• To investigate the fluid treatment and the occurrence of organ failure in severe TBI patients treated according to the ICP-targeted therapy with defined strategies for fluid treatment (paper II)

• To study the effect of prostacyclin versus placebo on cerebral metabolism in patients with severe TBI, by analysing the changes in the lactate/pyruvate ratio measured by cerebral microdialysis (paper III)

• To analyse the effect of prostacyclin versus placebo on the early systemic inflammatory response in severe TBI patients (paper IV)

• To investigate ADMA as a marker of endothelial dysfunction following aneurysmal SAH (paper V)
Patients and Methods

"Forget about faith! You didn’t need faith to fly, you needed to understand flying.”

Richard Bach
“Jonathan Livingston Seagull - a story”

PATIENTS & METHODS

The patients in this thesis were recruited to the studies from the ICU, Neurosurgery division at the University Hospital of Northern Sweden, Umeå (papers I - V) and the ICU, Neurosurgery division at Sahlgrenska University Hospital, Gothenburg, Sweden (paper I).

Papers I - IV focus on the patients with severe traumatic brain injury treated with an ICP targeted therapy and the effects of various parts of the therapy. The ICP-targeted therapy protocol was used in all patients in papers I–IV. Paper V focuses on endothelial dysfunction in patients with subarachnoid haemorrhage.

Ethical approvals were obtained from the Ethics Committee of the University of Umeå for paper I (Dnr; 03-173), paper II (Dnr; 04-141M), paper V (Dnr; 03-290) and papers III-IV (Dnr; 00-175) with approval from Läkemedelsverket for the pharmacological study of prostacyclin (Medical Products Agency Dnr; 151:633/01) Written informed consent was used in papers I and III –V.

Paper I focuses retrospectively on the outcome after an ICP-targeted therapy treatment. The implementation of the ICP-targeted protocol was quantified by analysing the achieved threshold. Children less than 15 years of age were included and treated by the ICP targeted therapy, during a ten year period. Medical records were retrieved with reference to blunt head trauma, ICP monitoring device and neurosurgery, and then retrospectively evaluated and analysed. Physiological and laboratory data were categorised according to protocol. Each parameter was evaluated and counted from the time of arrival at the ICU until removal of the ICP monitoring. Adherence to the protocol was quantitatively analysed for nine different subjects of the ICP-targeted treatment. Outcome was given in GOS.

Paper II focuses retrospectively on the fluid management of the predefined strategies according to the ICP-targeted therapy with special interest in albumin administration for organ failure and outcome. Fluid and drug administration and fluid loss was calculated for each patient per 24 hours during their stay at the ICU. Colloids (albumin, erytrocytes and plasma) and crystalloids balances were separated. Scoring suitable to injury at admission was done by APACHE II and ISS. Daily SOFA was scored during ICU stay for each patient to evaluate the development of organ failure. Outcome was given in GOS.

Papers III & IV are based on a prospective, double-blind, randomised and consecutive clinical study with patients treated with prostacyclin or placebo in addition
Patients and Methods

to the ICP targeted therapy. Randomisation was done by the means of the random number method and was blinded throughout the study period.

All personnel and investigators were blinded to the testdrug, which came from individual numbered containers with an identical appearance, prepared by the hospital pharmacy. Prostacyclin (epoprostenol, Flolan®, GlaxoSmithKline) was the active drug used, versus saline as the placebo, administered intravenously (0.5ng/kg/min). The prostacyclin/placebo (testdrug) infusion was started as soon as possible after arrival to the ICU and was continued for 72 hours, and then de-escalated during 24 hours.

From 1998 the additional treatment with the endogenous prostacyclin, epoprostenol, (Flolan®, GlaxoSmithKline) was added to the ICP-targeted therapy even in papers I and II.

Paper III is analysing cerebral metabolic markers such as lactate, pyruvate and glucose with cerebral microdialysis over time. It also studies the differences between prostacyclin versus placebo effects in severe TBI patients according to cerebral metabolism. One aspect was to analyse cerebral metabolism with microdialysis with the lactate/pyruvate ratio (L/P). The difference in effect of prostacyclin versus placebo of the lactate/puruvat ratio at 24 hours after the start of the test-drug was the end-point of the study. In paper III, an increase in the L/P ratio is accepted as a marker for ischemia (Enblad et al. 1996, Granholm and Siesjo 1969, Persson and Hillered 1992). To analyse the initial L/P was considered as a prognosis for outcome at three months. GOS was evaluated at three months post injury.

Paper IV is a part of the prospective, double-blind, randomised and consecutive clinical study with a focus on inflammatory response after trauma and severe TBI. Blood samples of cytokines were performed once daily for five days in a row, and were analysed by the ELISA method. CRP was sampled daily on a regular basis. Outcome was related to GOS at three months.

Paper V is a prospective, pilot study with angiographic verified ruptured aneurysms in patients with SAH. The patients were included during weekdays. At the time of sampling for ADMA in serum and in CSF, physiological parameters and laboratory parameters were obtained and documented. The first blood sample was taken within 48 hours of the debut of SAH. ADMA was analysed by a high-performance liquid chromatography (HPLC) method. All patients were treated with intravenous infusion of nimodipine (calcium receptor blocker). There was an age and sex match healthy control group from the database of the Monika-project, which is an epidemiological health evaluation (Stegmayr, Lundberg and Asplund 2003). Follow-up with ADMA analyses and outcome by GOS was done at three months after SAH debut.
Table 4. Schematic summary of the characteristics of studies included in this thesis.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Problem Approached</th>
<th>Design &amp; Setting</th>
<th>Patients</th>
<th>Period</th>
<th>Scoring</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Severe TBI, ICP-targeted therapy; Implementation &amp; Outcome</td>
<td>Retrospective clinical analysis, two centre study</td>
<td>41 children &lt; 15 years of age</td>
<td>1993-2002</td>
<td>GCS, RLS, ISS, GOS</td>
<td>Hb, Albumin, Glucose &amp; Sodium, ICP, CPP, SAT, BP, HR &amp; Temperature.</td>
</tr>
<tr>
<td>II</td>
<td>Severe TBI, ICP-targeted therapy; Fluid treatment &amp; Outcome</td>
<td>Retrospective clinical analysis, one centre study</td>
<td>93 adults, ≥15 ≤ 70 years of age</td>
<td>1998-2001</td>
<td>GCS, APACHEII, ISS, SOFA, ARDS/ALI, GOS</td>
<td>Hb, Albumin, Glucose &amp; Sodium, CVP, MAP &amp; HR, Quantity of fluids &amp; drugs</td>
</tr>
<tr>
<td>III</td>
<td>Severe TBI, ICP-targeted therapy; Prostacyclin, Cerebral Microdialysis &amp; Outcome</td>
<td>Prospective, Consecutive, Double blind, Randomised Clinical, one centre study</td>
<td>48 adults, ≥15 ≤ 70 years of age</td>
<td>2002-2005</td>
<td>GCS, APACHEII, ISS, GOS</td>
<td>Lactate / Puruvate ratio &amp; glucose by Microdialysis, ICP, MAP &amp; CPP</td>
</tr>
<tr>
<td>IV</td>
<td>Severe TBI, ICP-targeted therapy; Prostacyclin, Inflammatory response &amp; Outcome</td>
<td>Extended part of study III</td>
<td>46 adults, ≥15 ≤ 70 years of age</td>
<td>2002-2005</td>
<td>GCS, APACHEII, ISS, SOFA, GOS</td>
<td>IL-6, IL-8 &amp; sICAM by ELISA, CRP</td>
</tr>
<tr>
<td>V</td>
<td>Acute SAH, Markers of endothelial dysfunction</td>
<td>Prospective, clinical, one centre study</td>
<td>20 adults</td>
<td>2005</td>
<td>GCS, H&amp;H, Fischer, GOS</td>
<td>ADMA in serum &amp; CSF by HPLC, CRP</td>
</tr>
</tbody>
</table>
Patients and Methods

Inclusion criteria
1. Less than 15 years of age (paper I) or ≥15 to 70 years of age (paper II-IV).
2. Medical history of severe blunt head trauma (paper I-IV).
3. Arrival at University Hospital within 24 hours after injury (paper I-IV).
4. GCS ≤ 8 and/or RLS ≥ 3 at the time of sedation and intubation (paper I-IV).
5. Need for intensive care > 72 hours for survivors (paper I-IV).
6. Intubated due to head trauma before arrival at the ICU (paper I).
7. Patients with GCS 3 and/or bilateral, dilated and fixed pupil were included (paper I-IV).
8. Treatment according to the principles of the ICP targeted therapy (paper I-IV).
9. Angiographic verified aneurysm with subarachnoid haemorrhage (paper V).

Exclusion criteria
1. The first recorded CPP < 10 mmHg was considered dead on arrival (paper I-IV).
2. Penetrating head injury (paper I-IV).
4. Pregnant or lactating woman (paper III-IV).
5. Known bleeding disorders (paper III-IV).
6. Allergy to epoprostenol (paper III-IV).
7. Traumatic subarachnoid haemorrhage (paper V).

Table 5. Inclusion and exclusion criteria.
GCS = Glasgow Coma Scale; RLS = Reaction Level Scale; ICP = Intracranial pressure; CPP = Cerebral Perfusion Pressure.

Monitoring

Computerised tomography of the brain (CT-scan) was performed as soon as possible, and a second CT-scan performed within 24 hours after trauma. CT-scans were thereafter performed whenever necessary, depending on the patient’s condition. Physiological parameters such as ICP, CPP, MAP, heart rate, oxygen saturation (SAT), end-tidal CO₂, temperature and urinary output data were documented from the time of arrival at the ICU until removal of the intracranial pressure monitoring, (papers I-IV).

Bedside monitors collected parameters continuously in time sequences ranging from one per minute to one per hour (papers I-V).

Arterial blood pressure was measured invasively and the zero-pressure baseline was set at heart level. Arterial bloodgases including sodium and potassium were measured at the ICU using a standard blood gas analyzer, approved by the accredited University Hospital laboratory. Laboratory data for each study were analysed at the accredited University Hospital laboratory using standard, fully automated procedures (papers I-V).
Patients and Methods

All children had ICP monitoring with an intraparenchymal sensor (Camino 1993-1996, Codman MicroSensor™ 1996-2002) and/or an intraventricular catheter. ICP above 20 mmHg was the threshold for intervention and escalation of treatment. CPP down to 40 mmHg was allowed due to the young age of the patients. The patients were considered to have hypotension when systolic blood pressure was below $<70$ mmHg + 2 times of age (paper I). All adults had ICP monitoring with an intraparenchymal sensor (Codman MicroSensor™ 1998-2005) and/or an intraventricular catheter (papers II-IV). ICP above 20 mmHg was the threshold for intervention and escalation of treatment in severe TBI patients and CPP above 50 mmHg was considered to be standard (papers II-IV).

Ventricular drainage was used in patients when there was a risk of hydrocephalus and/or increased ICP (papers I - V).

Scoring

The RLS $\geq 3$ and GCS $\leq 8$ were used for assessment of severe TBI. (papers I-IV). Severity of illness and injury were scored by APACHE II and ISS at arrival at the ICU of the University Hospital. ISS $\geq 16$ was considered severe injury (papers I-IV). Organ failure was defined as SOFA $\geq 3$. The CNS was not scored due sedated and anesthetised patients (papers II & IV). In patients with SAH, the H&H score was used for evaluating severity and the Fisher score was used for estimating the degree of haemorrhage seen in the first CT-scan of the brain (paper V). GOS was used in all papers for outcome assessment (papers I-V).

Microdialysis

In paper III microdialysis was used for studying the cerebral metabolism by analysing the interstitial glucose, lactate and pyruvate components of the CNS.

Each patient received three microdialysis catheters as soon as possible after arrival and the decision of inclusion, made by the neurosurgeon on call for the study. The catheters were either CMA 70 with a gold tip or CMA 60 (CMA Microdialysis AB, Solna, Sweden). Two CMA 70 catheters were placed in the brain parenchyma bilaterally, according to a standardized scheme. The A-catheter was placed in the most severely injured hemisphere according to the CT-scan. The B-catheter was placed in the less injured hemisphere The C-catheter was placed subcutaneously in the upper part of abdomen.

“Perfusion fluid CNS” for catheters A and B, and “perfusion fluid T1” for catheter C (standards from the manufactures, CMA Microdialysis AB) was used with a standard infusion rate of 0.3µL/min. A sampling protocol was used. The first vial was discharged 0.5 – 1.5 hours after the start of microdialysis. The sampling interval was two hours, and the first sampling started at even hours after insertion of the catheters. The first collected sample was considered “zero-base-line” and was collected before the start of drug infusion. All samples were stored
Patients and Methods

frozen to -70°C and later analysed by the research nurse using the CMA 600 analyser (CMA Microdialysis AB).

Cytokines

In paper IV daily blood sampling of cytokines was performed. IL-6 and IL-8 were sampled due to their early response and relatively long half-life in serum. Analysis of sICAM-1 was done for its ability to mediate leukocyte-endothelial cell adhesion. Daily routine sampling of CRP was included and analysed as part of the pro-inflammatory response after trauma. Blood sampling was performed over five consecutive days after arrival to the University Hospital. The blood samples for cytokines were immediately centrifuged and serum was initially frozen in -20°C, and later stored in -70°C until the assays for cytokines were performed.

Analyses of cytokines were determined by the validated and established method, enzyme linked immunosorbent assays (ELISA) according to the manufacturer’s procedure. The levels of serum IL-6 pg/mL, IL-8 pg/mL (ELISA, Pierce Biotechnology Inc, Rockford, IL, USA) and sICAM-1 ng/mL (ELISA, Biosource International Inc, Camarillo, CA, USA) were determined. All samples were performed in duplicate. The values of IL-6, IL-8 and sICAM-1 are grouped within 24, 48, 72, 96 and 120 hours after trauma.

Asymmetric dimethylarginine

In paper V ADMA was analysed by the validated high-performance liquid chromatography (HPLC) technique, according to a minor modified method (Teerlink et al x 2, 2002, 2007). Blood sampling was performed over seven consecutive days after arrival to the University Hospital. Sampling from the ventricular drainage for CSF was performed according to the function of the drainage and the amount of CSF production per day. All samples for ADMA analyses were immediately centrifuged and was initially frozen in -20°C, and later stored in -70°C, until the analyses by HPLC technique were performed. At the three months follow-up there was a control of ADMA concentration in serum and GOS score.

C-reactive protein

Analyses of CRP were performed in papers IV-V at the accredited University laboratory of Umeå. The values of CRP are grouped within 24, 48, 72, 96 and 120 hours after trauma in paper IV.
“It is important to seek constantly for further knowledge, and to take the responsibility for the use of this knowledge. Naturally we have to try to help people even when we lack knowledge, but we must never act against our better judgement.”

Ancient Chinese proverb

**RESULTS & COMMENTS**

**Characteristics**

Trauma occurs as a result of accidents involving motor vehicles inclusive snowmobiles, falling from heights, pedestrians hit by a car or horseback riding accidents etc. ([papers I-IV](#)) (Table 6 and 7). There was trauma from blunt violence and abuse in the adult populations ([papers II-IV](#)). The occurrences of trauma in these materials are in accordance with the global distribution of the origin to TBI. Hyder et al describe that about 10% are due to blunt violence and abuse, about 10% are due to sports and work-related accidents, and an average of less than 30% are due to falls, which makes that about 60% are due to traffic accidents (Hyder et al. 2007).

<table>
<thead>
<tr>
<th>Paper</th>
<th>Traffic Accident</th>
<th>Fall Accident</th>
<th>Thoracic &amp; Abdominal Injury</th>
<th>Fractures</th>
<th>Cerebral Haematoma **</th>
<th>Cerebral Contusion / oedema ***</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>61%</td>
<td>27%</td>
<td>22%</td>
<td>39%</td>
<td>39%</td>
<td>93%</td>
</tr>
<tr>
<td>II</td>
<td>51%</td>
<td>38%</td>
<td>17%</td>
<td>41%</td>
<td>56%</td>
<td>89%</td>
</tr>
<tr>
<td>III *</td>
<td>69%</td>
<td>19%</td>
<td>54%</td>
<td>56%</td>
<td>58%</td>
<td>85%</td>
</tr>
</tbody>
</table>

* total population ; ** Subdural and/or epidural haematoma at first CT-scan; *** at first CT-scan

Table 6. Accident and Injury data from studies I-III

All patients except two (182 patients totally) had pathological findings at the first CT scan of the brain ([papers I – IV](#)). The panorama of brain injuries included SDH, EDH, contusions, oedema complicated with midline-shift, CT verified skull fractures and traumatic SAH.

**Paper IV** describes that major surgery was performed within 48 hours from the trauma 52% in the prostacyclin group versus 61% in the placebo group. 78% in each group had surgery performed at some time during their ICU stay. In the placebo group only neurosurgery was performed. In the prostacyclin group, besides neurosurgery there was also facial fracture reconstruction and major orthopaedic surgery.
Results and Comments

Paper V describes the aneurysms of the cerebral circulation. Confounding diseases of hypertension (50%), cardiovascular diseases (25%), hyperlipidemi (20%) and smokers (55%) were found in the study group.

<table>
<thead>
<tr>
<th></th>
<th>Paper I</th>
<th>II</th>
<th>III *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender m/f **</td>
<td>26/15</td>
<td>71/22</td>
<td>31/17</td>
</tr>
<tr>
<td>Age***</td>
<td>8.4 ±4.1</td>
<td>37.6 ±16.1</td>
<td>35.5 ±2.2</td>
</tr>
<tr>
<td>GCS****</td>
<td>7(3-8)</td>
<td>7(3-8)</td>
<td>6(3-8)</td>
</tr>
<tr>
<td>ISS****</td>
<td>25(16-75)</td>
<td>18(9-43)</td>
<td>29(9-50)</td>
</tr>
<tr>
<td>APACHE II***</td>
<td>X</td>
<td>19(9-27)</td>
<td>20.5(12-32)</td>
</tr>
<tr>
<td>Multi-trauma %</td>
<td>58</td>
<td>42</td>
<td>69</td>
</tr>
</tbody>
</table>

* Total population; ** number; *** mean ±SD; **** median (range);
GCS = Glasgow Coma Scale; ISS = Injury Severity Score;
APACHE II = Acute Physiologic and Chronic Health Evaluation II

Table 7. Demographic data from studies I-III

Management and treatment results

Physiological parameters

Paper I showed statistical significance between survivors and non-survivors in maximal ICP and minimal CPP during ICU treatment period.

In paper II parameters of mean ICP, CPP, MAP, heart rate, and PaCO₂ between days one to ten were all within normal limits for adults. In papers III and IV, there was no statistical significance between the prostacyclin versus the placebo group concerning mean ICP, mean CPP and mean MAP values. Mean ICP and mean CPP were well within the preset treatment goals during the treatment period of 120 hours at the ICU. Values recorded once per minute showed that less than 3% of ICP were above 20 mmHg, and less than 3% of CPP values were below 50 mmHg.

Implementation

Paper I shows the success rate of fulfilled thresholds according to the preset goals of the protocol (Table 8). All values were accounted for and the total numbers of observations were 34,930. Pathological thresholds were observed on 2932 occasions. A total of 8.4% of all values recorded were beyond threshold limits according to the protocol.

Paper II shows that the mean values according to the protocol for serum sodium, albumin, Hb and blood glucose were kept within protocol limits. No sig-
Results and Comments

Significant differences were found during days one to four between survivors and non-survivors.

Papers IV had no statistical difference between the groups of prostacyclin versus placebo concerning WBC, Hb, fibrinogen, antithrombin II, APTT and platelets. Body temperature was calculated as the mean of the highest temperature /day, without significant difference between the groups.

<table>
<thead>
<tr>
<th>Pathological Threshold values</th>
<th>Total No. of observations</th>
<th>No. of pathological observation</th>
<th>% of pathological observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP &gt; 20 mmHg</td>
<td>7909</td>
<td>1268</td>
<td>16</td>
</tr>
<tr>
<td>CPP &lt; 40 mmHg</td>
<td>7753</td>
<td>303</td>
<td>3.9</td>
</tr>
<tr>
<td>Hypotension**</td>
<td>8221</td>
<td>44</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypoxia &lt; 90 % saturation</td>
<td>2839</td>
<td>10</td>
<td>&lt; 0.4</td>
</tr>
<tr>
<td>Hyperthermia &gt; 38º C</td>
<td>2785</td>
<td>547</td>
<td>19.6</td>
</tr>
<tr>
<td>B-glucose &lt; 3 &gt; 8 mmol/L</td>
<td>1622</td>
<td>162</td>
<td>10</td>
</tr>
<tr>
<td>S-sodium &lt; 135 &gt; 150 mmol/L</td>
<td>1681</td>
<td>114</td>
<td>7</td>
</tr>
<tr>
<td>S-albumin &lt; 35 g/L</td>
<td>250</td>
<td>23</td>
<td>9.2</td>
</tr>
<tr>
<td>Hb &lt; 110 g/L **</td>
<td>1870</td>
<td>461</td>
<td>24.6</td>
</tr>
</tbody>
</table>

** Age related values

Table 8. Observations of threshold values during 10 days of intensive care for paediatric patients. ICP = Intracranial pressure; CPP = Cerebral perfusion pressure; No = number; Hb = Haemoglobin

Fluid management

Analysis of fluid treatment in paper I show a total fluid balance with a plus balance of 2 ml/kg/patient for survivors. The total fluid balance for non-survivors was plus 53 ml/kg/patient.

In paper II, the total fluid balance was positive days one to three, and negative days four to ten. From day two, the balance of crystalloids showed a negative trend. From day three and onwards, the quantities of crystalloids were in the range of 30-35 mL/kg/day. Thus the patients received crystalloid fluids in the amounts of basal needs. Patients were treated with both 4%-albumin and hyperoncotic 20%-albumin. The distribution of 4%-albumin was 45% as opposed to hyperoncotic 20%-albumin, which was 55%. Total amount of colloids constituted between 40-60% of the total fluids in mL given per day. About 20% of the total amount of volume substituted days one and two were erytrocyte transfusions. Non-survivors
Results and Comments

received statistically significant more erytrocytes and albumin in mL than survivors.

Paper IV shows that the total fluid volume given as mean ml/patient was not significantly different between the prostacyclin and placebo groups.

Pharmacology treatment

The investigation of the drug used during ICU care, in paper I, shows that all children (100 %) had continuous infusion of midazolam & fentanyl during mechanical ventilation. 88% of the children received pentothal during mean 6.8±3.7 days, 83% received clonidine for 7.6±4.4 days and 76% received metoprolol for 6.7±4.2 days. 32% received low-dose prostacyclin infusion, 24% received DHE infusion and 27% required short-acting insulin. 80% received diuretics. Vasoactive drugs were used 5.7±3.5 days in 34%. There was an overlap among vasoactive drugs and metoprolol/clonidine infusions in 20%.

Paper II shows that day two had the most abundant vasopressor support in 28% of the patients, and day three had the most abundant diuretic support for 70% of the patients. Vasoactive drugs were withdrawn as quickly as possible, and were rarely used after day six in the ICU. Figure 6 shows the percentage of patients that received different drugs at some time during the ICU period of ten days.

![Figure 6. Pharmacological treatment during ten days of ICU care.](image-url)
Results and Comments

Prostacyclin

In the clinical studies of papers I-IV, 125/182 patients received prostacyclin. No complication related to the prostacyclin infusion has been observed. In papers III & IV, no difference is noticed in outcome, organ failure or fluid balance in patients treated or not treated with prostacyclin. There was no significant difference in median (range) between the groups, concerning the time from trauma to start of prostacyclin/placebo infusion. The prostacyclin/placebo infusion was started as soon as possible after arrival.

Microdialysis

In the results from paper III, brain microdialysis revealed no statistical significant differences between the prostacyclin group and the placebo group regarding time of trauma to implantation of the microdialysis catheters.

There was an apparent decrease in the L/P ratio when comparing the null-sample and the sample at 24 hours in A- and B-catheters, but no statistical difference between the prostacyclin and placebo groups. Statistical difference was seen in the A-catheter from null sample to 24 hours by a reduction of L/P ratio. The B-catheter showed no significant L/P ratio reduction over time. The initial L/P ratio did not prognosticate for outcome.

There was no significant difference in brain glucose levels between the two groups or in the total population between the A- and B -catheters. The subcutaneous glucose in the total population showed elevating concentrations from the initial value of 3.6 ± 0.4 mmol/L and after 24 hours the value was 4.9 ± 0.3 mmol/L (p< 0.0001).

Inflammatory response in severe TBI patients

Analyses in paper IV of cytokines in the patients treated either with prostacyclin or placebo showed no statistical differences regarding IL-6, IL-8 and sICAM-1 within 24 hours after trauma and before the start of prostacyclin/placebo infusion.

The prostacyclin group had significantly lower IL-6 concentrations within 96 hours after trauma compared to the placebo group (p<0.05). IL-6 concentrations in the prostacyclin group decreased significantly from within 48 hours to within 96 hours and to within 120 hours (p<0.05) after trauma.

Neither sICAM-1 nor IL-8 concentrations showed a significant difference neither between groups nor over time. The levels of sICAM-1 were not significantly different between the prostacyclin and the placebo groups even though there was a tendency for a lower expression of sICAM-1 in the prostacyclin group during the administration of the testdrug.

CRP ranged from 10g/L to 490g/L during a period of 24 to120 hours post-trauma in all patients. The prostacyclin group had significant lower CRP within 96
Results and Comments

hours \((p<0.04)\) and within 120 hours \((p=0.008)\) after the accident compared to the placebo group.

**ADMA and inflammatory response in SAH patients**

**Paper V** shows that CRP and ADMA in serum increased in the acute phase after SAH, and that ADMA remained elevated after three months. The massive systemic inflammatory process after SAH induces an increase in inflammatory markers of CRP, and the inflammation in turn could cause endothelial dysfunction, which can be indicated by an increase in ADMA.

ADMA in serum gradually increased by 68% from day two to day seven \((p<0.05)\). This elevation of ADMA in serum was still present at the three month follow-up. There was no significant difference in ADMA in serum from day seven to the three month follow-up \((n=15)\).

CRP and ADMA increased statistically significant \((p<0.05)\) during the first week after SAH. CRP was elevated earlier than ADMA in acute phase.

**Organ failure**

In **papers II & IV**, the most dominant result was observed in respiration, according to SOFA scores. More than 30% of the patients had a SOFA score more than three based on all observed parameters of respiration. In **paper II** ARDS and ALI, were observed in 18% of all patients (Bernard et al 1994). No patients in **papers II – IV** developed renal failure, but liver and coagulation dysfunction was sparsely seen.

The prostacyclin group in **paper IV** is shown to have a tendency to recover from respiratory failure, SOFA ≥ 3, earlier than placebo group over time, but there was no statistical significant difference between the groups (Figure 7).

![Figure 7](image-url)

**Figure 7.** SOFA score of respiration in prostacyclin versus placebo groups. Scores are summed 0-2 and 3-4 in each group. SOFA = Sequential Organ Failure Assessment
Results and Comments

Outcome

In paper I 83% of the children were referred from regional hospitals. Pre-hospital, regional hospital care including transportation managed to transfer the children from the accident site to the University Hospital within a median of five hours (0.5-26). The children showed favourable outcome (GOS 4 + 5) in 80% of the cases. Three deaths were recorded by the time of follow-up, median 12 months (2.5 – 22) after trauma. The deceased children did not survive the ICU period. Mortality rate was 7%.

In paper II the mortality at 28 days follow-up after trauma was 11% in 93 severe TBI patients. Favourable outcome (GOS 4 + 5) was 63%. Ten non-survivors had statistically significant higher APACHE II and ISS scores ($p \leq 0.05$) and statistically significant lower GCS scores ($p \leq 0.05$) and thereby were considered more traumatized compared to the 83 survivors.

In paper III the time from accident until admission was mean 6.2±0.7SEM hours. Time from accident until implantation of microdialysis catheters was mean 12.2±0.7SEM hours. Favourable outcome at three months post injury was 52% in total the population. The mortality rate was 13%.

In paper IV the median time from accident to the first blood sample of cytokines was 16.5 (6-32) hours in the prostacyclin group versus 12 hours (5-37) in the placebo group. At three months follow-up, favourable outcome (GOS 4 + 5) was 57% in the prostacyclin group versus 48% in the placebo group. Mortality in the prostacyclin group was 9% versus 17% in the placebo group, but no statistical significance was revealed between groups.

In paper V outcome at three months showed a median GOS 5 (range 1-5).

Papers I – IV demonstrate a high favourable outcome, between 52% - 80% according to GOS 4 + 5 and a survival rate between 78 - 93% in patients treated according to the ICP-targeted protocol (Figure 8).

![Figure 8. Outcome according to Glasgow Outcome Scale](image-url)
DISCUSSION

Severe cerebral emergencies provoked by trauma or vascular disease will initiate a number of responses. There will be systemic inflammatory reactions and activation of the systemic cascade systems with the risk of developing endothelial dysfunction. The central nervous system reacts with degrees of altered cerebral blood flow, disrupted blood-brain barrier, increased intracranial pressure, focal or diffuse ischemia, hemorrhage, necrosis, and neuron dysfunction.

The expression “Talk and die” was used among neuroscientists in Glasgow during the 1970s and described patients who had been awake at arrival after TBI and then suddenly died. The deaths were due to avoidable factors and to secondary brain injuries (Rose, Valtonen and Jennett 1977). The term "Golden Hour" is used to characterize the urgent need for the care of trauma patients. This term implies that morbidity and mortality are affected if care is not initiated within the first hour after trauma (Lerner and Moscati 2001).

In summary, the thesis includes treatment strategy for severe TBI patients based on physiological principles according to the protocol of the ICP-targeted therapy. Four studies evaluate protocol implementation, fluid strategies, effect of prostacyclin, inflammatory and endothelial dysfunction markers for patients with severe TBI. One study analyse the endogenous production of endothelial dysfunction and inflammatory markers in acute SAH patients. The patients included had acute severe cerebral emergencies due to trauma or vascular disease, from 3 months to 70 years of age with both pro- and retro- perspectives from 1993 to 2005.

Paediatric patients with severe TBI showed a very good outcome with a survival rate of 93% and a favourable outcome (GOS 4 + 5) of 80% (Paper I). Studies from the same period but with different aspects of treatment such as hyperventilation, decompressiv craniectomy, hypertonic saline, and neuromuscular paralysis for severe TBI children and with long-time follow-ups describe mortality rates from 18% to 33% (Thakker et al. 1997) (Taylor et al. 2001, Downard et al. 2000, Hackbarth et al. 2002, Khanna et al. 2000, Jones et al. 2003, White et al. 2001)

A recently published study with an ICP-targeted therapy used in 48 children with severe TBI had a favourable outcome (GOS 4 + 5) of about 90% after six months (Grinkevičiūte et al. 2008). Our results match these recently published studies (Wahlström et al. 2005). Two other newly published studies of paediatric populations treated according to two different protocols showed less favourable outcome. There was either an “in-hospital” mortality of 25% or a favourable outcome (GOS 4 + 5) of 58% at six months follow-up (Vavilala et al. 2006, Jagannathan et al. 2008).

There are international guidelines for the treatment of TBI in children. The main similarities between the Paediatric Guidelines of 2003 and the ICP-targeted therapy
used in paper I are ICP and CPP thresholds. The main differences are the use of neuromuscular blocking drugs and fluid therapy recommendations in the Paediatric Guidelines of 2003 (Table 9)

<table>
<thead>
<tr>
<th>Topic</th>
<th>Guidelines 2003</th>
<th>ICP-targeted therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP - monitoring</td>
<td>Option</td>
<td>Obligatory</td>
</tr>
<tr>
<td>ICP threshold</td>
<td>Option ICP &lt; 20 mmHg</td>
<td>ICP &lt; 20 mmHg</td>
</tr>
<tr>
<td>CPP threshold</td>
<td>Guidelines CPP &gt; 40 mmHg</td>
<td>CPP &gt; 40 mmHg</td>
</tr>
<tr>
<td>Sedation &amp; Analgesia</td>
<td>Option</td>
<td>Obligatory</td>
</tr>
<tr>
<td>CSF - drainage</td>
<td>Option</td>
<td>Option</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Option, high-dose treatment</td>
<td>Option, Low-dose treatment</td>
</tr>
<tr>
<td>Temperature</td>
<td>Option, avoid hyperthermia</td>
<td>Normothermia, avoid hyperthermia</td>
</tr>
<tr>
<td>Craniectomy</td>
<td>Option</td>
<td>Option</td>
</tr>
<tr>
<td>Neuromuscular blockers</td>
<td>Option</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Fluid therapy</td>
<td>Not considered</td>
<td>Normovolemia &amp; colloid treatment</td>
</tr>
<tr>
<td>Hyperosmolar therapy</td>
<td>Option, Mannitol, HTS</td>
<td>Not recommended but Mannitol in emergency situation</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>Option, avoid prophylactic hyperventilation</td>
<td>Only once in emergency situation</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Option</td>
<td>Recommended</td>
</tr>
<tr>
<td>Steroids</td>
<td>Option, Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Anti-seizure prophylaxis</td>
<td>Guidelines, Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

Table 9. Comparison of Pediatric Guidelines 2003 and ICP-targeted therapy
ICP = Intracranial pressure; CPP = Cerebral perfusion pressure; CSF = Cerebrospinal fluid

This is a comparison of the Paediatric Guidelines 2003 and the ICP-targeted therapy. The degree of certainty associated with a particular recommendation in the paediatric guidelines is connected to classification of evidence from available data.
Standards are based on class I evidence (randomized controlled trials) or on strong class II. Guidelines are based on class II evidence (observational or cohort studies) or on strong class III. Options are class III evidence (retropective data, databases) (Carney et al. 2003).

The ICP-targeted therapy protocol adherence was 90% in our paediatric study. Protocol compliance is necessary for outcome results, and adherence should be continuously evaluated. Markedly improved outcome is shown by the ability to follow a protocol (Fakhry et al. 2004, Persson and Enblad 1999, Elf et al. 2002, Eker et al. 1998).

The ICP-targeted therapy includes strategies to maintain normovolemia to ensure an adequate cerebral blood flow for the necessary delivery of oxygen and glucose to the injured brain (Papers I – IV). Normovolemia is maintained mainly by colloids. The normovolemia is based on clinical evaluations of physiological parameters. The thresholds used in the ICP-targeted therapy use the normal limits of laboratory parameters for haemoglobin, albumin and sodium. In guidelines or in the literature, there are no golden standards for evaluating normovolemia or which thresholds to use to optimise osmotic and homeostatic status in critically ill patients (Hébert et al. 1999, Heier et al. 2006).

The ICP-targeted therapy aims at maintaining normal intravascular oncotic pressure by normal limits of albumin and to increase oxygen delivery by erythrocyte transfusions. Thereby preventing and reducing brain oedema formation. The thresholds according to the protocol of concentrations in plasma of albumin, Hb and sodium are therefore probably relevant in that aspect, since we can demonstrate high favourable outcomes (Eker et al. 1998, Naredi et al. 1998, Naredi et al. 2001, Wahlström et al. 2005, Olivecrona et al. 2007).


Reduced oxygen transportation is deleterious for a vulnerable brain. Erythrocytes are oxygen carriers, and affect osmotic pressure and increase oxygen tension. In experimental studies, animals with anaemia and TBI develop impaired cerebral autoregulation, cerebral contusions and reduced cerebral oxygen tension and thereby creating a manifest damaged brain parenchyma (DeWitt et al. 1992, Glass et al. 1999).

One prospective, randomised controlled clinical study has evaluated a liberal versus a restrictive erythrocyte transfusion threshold (70-90g/L versus 100-120g/L)
in a critically ill patient population. The results showed no difference in mortality or adverse effects. Due to safety aspects, the recommendation was a restrictive approach. The sub-analysis of severe TBI patients showed a trend with lower mortality in the group that received the liberal amount of erythrocyte transfusions (Hébert et al. 1999, McIntyre et al. 2006).

Two studies have demonstrated an increase in brain tissue partial pressure of oxygen (PtiO$_2$) when erythrocytes are transfused to patients. The normal levels of PtiO$_2$ were preserved for an average of 24 hours after transfusion (Leal-Noval et al. 2006, Smith et al. 2005).

Albumin increases osmotic pressure, decreases transcapillary filtration, and decreases oedema. Treatment with albumin in clinical settings has been debated over the years. Albumin was related to a 6% excess of deaths above control in a meta-analysis from 1998, but since then there has been no prospective double blinded clinical trial that has confirmed these findings. This meta-analysis was assessed from heterogeneous studies with different end-points, ages, protocols and severity of diseases and it has been questioned (Cochran 1998). Another meta-analysis which evaluated randomised controlled trials of albumin versus crystalloid treatment. The analyse showed that there was no effect on mortality by albumin treatment in comparison to crystalloid treatment. The evaluation supported the safety of albumin treatment (Wilkes and Navickis 2001). Human albumin is considered a safe drug with very rare serious adverse events and in 112 million doses no death was connected to the specific albumin administration (Vincent, Wilkes and Navickis 2003).

A large randomised trial compared 4% albumin versus saline in the treatment of 6997 heterogeneous critically ill patients at 16 hospitals in Australia and New Zealand. This study could not find any significant difference in mortality between the albumin and saline volume resuscitated groups (Finfer et al. 2004). Concerning the use of albumin in severe TBI, a post-hoc analysis of the same study of patients with severe TBI reported a higher mortality rate in patients assigned to albumin compared to those assigned to saline (Myburgh et al. 2007). Arguments against the sub-analysis could include: only an average of 76 % of severe TBI patients had ICP-monitoring devices, an additional 23 patients were included after the closing stages of the original study, and no information about treatment standard was included. The frequencies of the use of vasopressor drugs or diuretics were not given.

The hydrostatic capillary pressure is dominating as the driving force and the size of extravascular protein leakage is dependent on the capillary membrane permeability. The passive transport of proteins through the larger pores will increase simultaneously with the transcapillary loss of fluid (Rippe and Haraldsson 1994). The 20% hyperoncotic albumin in contrast to the 4% albumin has treatment favours. It has been shown that 20% hyperoncotic albumin in combination with furosemide has a superior effect in brain oedema treatment compared to the 4%
albumin (Albright et al. 1984, Belayev et al. 1998). Both the volume infused and the hydrostatic pressure is of importance when to consider the risk of oedema formation.

The use of vasopressors such as norepinephrine and phenylephrine may induce acute respiratory failure in patients with severe brain injury. Even renal failure and ischemic injury of the intestines can be affected by vasoconstrictive therapy (Holland et al. 2003, Martin et al. 2005, Rassler et al. 2003, Contant et al. 2001).

The human neutrophil activation and adhesion vary, depending on the type and amount of resuscitation fluid used in healthy volunteers. Crystalloids and artificial colloids significantly increased the activity of neutrophils, 12-18 times above baseline, but with 5% albumin there was a rise of only 2.2 times of the baseline values. Administration of 25% albumin showed no increased intracellular activity as a response to neutrophil action. The effect was dose-responsive and not due to dilution (Rhee et al. 2000). The effect of resuscitation fluids on the immunological response system has not been examined extensively.

Administering prostacyclin is done as an attempt to improve the cerebral microcirculation due to severe TBI (Papers III & IV). Prostacyclin affects the leucocytes and platelets adhesions, and vasodilate capillaries in injured brain tissue. It is important to lower the pre- and post-capillary resistance equivalent, to avoid an imbalance in hydrostatic pressure surrounding the capillary membrane.

That prostacyclin decreases the microvascular permeability has been reported from experimental settings of traumatic brain injury (Bentzer, Holbeck and Grände 1999, Bentzer, Kongstad and Grände 2001a, Bentzer et al. 2001b, Möller and Grände 1997, Möller and Grände 1999b, Möller and Grände 1999a). The indication to use prostacyclin as a treatment in severe TBI patients is that the balance between tromboxane A2 and prostacyclin shifts to tromboxane A2 in trauma situations (Moncada and Vane 1979b, Moncada and Amezcua 1979, Gryglewski et al. 1978). This might lead to the activation of microaggregation in platelets, capillary vasoconstriction and the activation on leukocytes’ adhesion to the endothelium. Together these mechanisms will impair microcirculation and increase capillary membrane permeability.

To administer prostacyclin in endogenous concentrations was considered due to the results from two different studies demonstrating positive trends in severe TBI patients. One of the studies included five patients with severe TBI where a positive effect on metabolic substances measured by brain microdialysis was demonstrated. The L/P ratio was reduced during the time of prostacyclin administration. A low-dose of prostacyclin is considered when no systemic vasodilatation is seen. The dose used (0.5 ng/kg/min) was considered to be in the range of endogenous production (Grände et al. 2000). Our study with prostacyclin versus placebo showed no statistical differences between the groups in L/P ratio after 24 hours controlled with brain microdialysis.
In the total population as well as in the prostacyclin and placebo groups, respectively, the initial L/P ratio was elevated at levels more than 40, which is considerably higher than the presumed normal value of 20, and could thereby indicate compromised microcirculation (Reinstrup et al. 2000).

Severe TBI activates inflammatory response (Paper IV). Post-traumatic inflammatory changes are believed to contribute to neuronal degeneration (Morganti-Kossmann et al. 2002). IL-6 is considered to be a potential predictor for the severity of head injury. High concentrations of IL-6 have shown to be a predictor of short-term prognosis and complications in head injured patients (Woiciechowsky et al. 2002). IL-6 levels decreased significantly faster in patients with less severity of head injury on admission than those with more severe head injury (McClain et al. 1991). This phenomenon is also shown in 45 children with brain injuries, with an early peak of IL-6 at 4 hours after trauma, and with a variety in the observed values according to injury severity (Kalabalikis et al. 1999). Early peak levels of IL-6 are also shown after prostacyclin administration in an experimental study, followed by a decrease over time. One plausible explanation could be that prostacyclin might directly stimulate IL-6 production in cells. (Ohta et al. 2005). We could not show any prediction of severity correlated to IL-6 concentrations. CRP concentrations correlated significantly to IL-6 concentrations and thereby confirmed the knowledge of IL-6 stimulating CRP production.

IL-8 levels showed no significant difference between the prostacyclin and the placebo group. IL-8 was not affected by prostacyclin treatment. This could be explained by the fact that elevated IL-8 concentrations in serum are an expression of inflammation, not an expression for endothelial reactions.

Given the consideration that prostacyclin influences leukocyte-adhesion to the vascular endothelium sICAM-1 was analyzed based on its ability to mediate leukocyte transmigration. Prostacyclin effects on sICAM-1 are not elucidated in severe TBI patients. Prostacyclin hinders the leucocytes from adhering to the endothelium, and thereby the sICAM-1 cannot stimulate the transmigration. Theoretically, the sICAM-1 expression might be decreased of prostacyclin. This was not obvious but our results showed a tendency on decreased levels of sICAM-1 in the prostacyclin group.

In order to improve outcome, there has been several studies with severe TBI using different treatment modalities but the results have been negative. Hypothermia was tested in children and in adults with severe TBI (Clifton 1995, Hutchison et al. 2006). The results demonstrate a significant increase in mortality and unfavourable outcome in the hypothermia group versus the group with normothermia.

In a randomised controlled trial examining death and disability after TBI methylprednisolone versus placebo treatments were evaluated. Mortality rate at 14 days post injury and disability at six months after trauma was higher in the group
that received cortisone compared to placebo (Edwards et al. 2002, Roberts et al. 2004). Magnesium as a treatment for moderate to severe TBI patients in a randomised, controlled trial was not considered to be neuroprotective and even had a negative effect, with risk of pulmonary oedema and respiratory failure (Temkin et al. 2007).

There was a high favourable outcome among the severe TBI patients treated according to the ICP-targeted thearapy (papers I - IV). No organ failure was elucidated more than for respiratory failure in about 30%. There was high favourable outcome in the study with albumin in combination with normovolemia (Paper II).

The outcome results in paper IV showed that twice as many died in the placebo group than the prostacyclin group. There was also a significant effect on pro-inflammatory response in the prostacyclin group.

A systemic inflammatory response has been described as a complicating factor in acute SAH which can lead to endothelial dysfunction (Paper V). Elevated ADMA concentrations in serum are involved during the later part of the acute phase of SAH. These levels stay elevated during the convalescent period after SAH, in three months. This might signal a systemic reaction of endothelial dysfunction. It is also shown that elevated ADMA in CSF is related to cerebral vasospasm in an experimental setting (Pluta 2004, Jung 2005). ADMA is known to be elevated in chronic vascular diseases. The massive systemic inflammatory process after SAH induces an increase in inflammatory markers such as CRP, and inflammation could cause endothelial dysfunction indicated by an increase in ADMA (Rothoerl et al. 2006, Cooke 2000). The relative importance of ADMA and CRP as cardiovascular risk factors remains to be evaluated and the relationship between inflammation and endothelial dysfunction needs to be investigated further (Ferri et al. 2007, Smith 2007).

Limits

Clinical settings are limited in the number of patients who can be included during a specific time range. Clinical studies both retrospective and prospective analysis have a risk for errors due to loss of data. There are difficulties to interpret drug effects in heterogenous populations and evaluate dose-repons reactions.

Interpretation of microdialysis data can be due to where the catheters are placed, how early the analysis are done after sampling period and freezing period of samples. The use of microdialysis and concentrations of metabolic substances in clinical conditions has to be verified.
CONCLUSIONS

- The ICP-targeted therapy protocol is applicable in all ages of patients with severe traumatic brain injury. Protocol adherence is exceptionally high.
- The ICP-targeted therapy has a high favourable outcome and low mortality, in comparison to other treatment protocols.
- The fluid treatment strategies of the ICP-targeted therapy are not associated with multi-organ failure.
- Prostacyclin does not affect the cerebral metabolism (lactate/ pyruvate) in severe TBI patients measured by microdialysis. Prostacyclin affects the inflammatory cascade by decreasing pro-inflammatory responses after trauma.
- Treatments with prostacyclin in endogenous concentrations showed no adverse effects on patients with severe traumatic brain injury treated at the Intensive Care Unit.
- ADMA increases after SAH and remains increased three months after the SAH. This implies that SAH can induce long-lasting endothelial dysfunction.

FUTURE CONSIDERATIONS

Modulation of the inflammatory endogenous substances might minimise endothelial dysfunction. The understanding of and the ability to treat endothelial dysfunction in severe cerebral emergencies with endogenous substances could be viewed as a future area of exploration.

Optimal transfusion strategies and the use of alternative fluids in severe traumatic brain injured patients are areas to explore.

Treatment of brain oedema after severe traumatic brain injury with or without haemorrhagic contusions is a cornerstone in treatment management for the future. Prevention of secondary brain injury may depend on giving a mixture of novel agents that modify destructive biochemical and inflammatory pathways, each having a potential therapeutic window possibly in different subgroups of patients.

"Läkarens tid upptages till den grad av tekniska uppgifter, att han måste lämna religionens utövning I andras, mera kompetentas händer. Läkaren måste inskränka sig till att genom sin personlighet och sina medicinska kunskaper söka trösta och lugna den sjuke. Vinner han därunder de sjukas hela förtroende har han emellertid därmed verkat som själsöjrare i modern mening."

Docent, Överläkare Arnold Josefson, "Husmoderns Läkarbok", 1928
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Svårt traumatisk skallskada och brustet pulsåderbråck i hjärnan (Subarachnoidal blödning) är två akuta tillstånd som kan leda till kvarstående svåra hjärnskador eller död. De som drabbas är relativt unga individer. Medelåldern vid svår traumatisk skallskada är mellan 25-35 år och vid pulsåderbråck är medelåldern runt 55 år.

Svår traumatisk skall skada orsakas av trubbigt våld mot huvudet med skador direkt på hjärnan, och anges som djup medvetlöshet pga. förhöjt tryck inne i skallen.

Den plötsligt påkomna bristningen i ett pulsåderbräck i hjärnan ger en plötsligt påkommen, mycket svår huvudvärk med efterföljande påverkan på flera organ i kroppen. Patienten kan antingen vara vaken eller djupt medvetlösh till följd av det brustna åderbracket.

De bestående skadorna hos den drabbade individen kan bero av flertalet orsaker. I första hand är det den direkta skadan på hjärnan vid det akuta tillfället som kan ge bestående men. I andra hand kan svullnad, dålig cirkulation och påverkan på ämnesomsättning i hjärnan leda till ytterligare skador.

I Umeå behandlas patienter med svår traumatisk skallskada enligt ett speciellt protokoll som kallas för ”Lundamodellen”, en s.k. intrakraniellt tryckstyrkt terapi. Den introducerades i Lund 1993 av professor Grände och hans kollegor och i Umeå började man använda motsvarande protokoll redan samma år.

Behandlingsprinciperna i protokollet baserar sig på fysiologiska förhållanden. Det innebär att man försöker reglera hjärnans volym inne i skallen och därmed reglera en eventuell tryckstegning som kan uppkomma pga. svullnad eller blödning i samband med våld mot huvudet. Protokollet innehåller en rad steg i syfte att behålla en normal cirkulation i hjärnan genom att förhindra utvecklingen av svullnad. Genom att bevara en adekvat cirkulation i hjärnan kan syrgas och näringsämnen levereras till hjärnans celler och därmed undvika ytterligare skador. Övervakning av trycket inne i skallen sker med hjälp av en tryckmätare placerad i hjärnan. Alla patienter vårdas med respirator och får läkemedel enligt ett protokoll. Neurokirurgi är en viktig del i protokollet för reglering av bland annat uppkomna blödningar i hjärnan.

Behandlingsmodellen används bland annat på Universitetssjukhusen i Lund, Göteborg och Umeå. De har rapporterat låg dödlighet i svåra traumatiska skallskador (ca 15 %) och låg förekomst av neurologiska kvarstående men. Ett år efter svår traumatisk skallskada är ca 70 % av patienterna helt oberoende av sjukvård. I en internationell jämförelse är detta ett mycket bra resultat. Även de patienter som klara sig utan sjukvård efter svår skallskada har dock ofta vid närmare undersökning en hel del neurologiska problem. Det är därför viktigt att tidigt i akut skede
förbättra hjärnans cirkulation och hindra pålagring på redan uppkomna skador, s.k. sekundära hjärnskador.

Vid våld mot kroppen aktiveras en kedjereaktion i kroppens inflammatoriska svar. Kedjereaktionen sätts igång av ämnen som frigörs vid skadan och leder bland annat till ansamling av vita blodkroppar och blodplättor i det skadade området. Detta kan dock, paradoxalt nog försämra mikrocirkulationen i området. I vissa fall kan det inflammatoriska svaret därför få ogynnsamma effekter och orsaka mer skada än nytta.

I kroppens kärlväggar produceras olika ämnen. Prostacyklin är ett av dessa ämnen och har som uppgift att minska de vita blodkroppar vidhäftningsförmåga till varandra, och till kärlväggen. Prostacyklin minskar blodplättarnas ihopklumpningsförmåga, och därmed minska risken för blodproppar. Övriga egenskaper är vidgning av blodkärl och förhindrande av vätskeutträde från blodbanan vid skada. Dessa effekter skulle sammantaget kunna vara fördelaktiga och förbättra cirkulationen i t.ex. hjärnan efter skada och på så sätt underlätta leverans av syrgas och näringssämen till nervcellerna. Prostacyklin finns som läkemedel.

Ett annat ämne som produceras i kärlväggens celler vid skador, inflammation och olika sjukdoms tillstånd är assymmetriskt dimetylarginin (ADMA). ADMA har som uppgift att minska mängden av ämnet kvävemonoxid. En ökad mängd ADMA tillsammans med en minskad mängd kvävemonoxid leder till att kärlen avsmalnar i omfång (kärlsammandragning). Detta kan in i sin tur leda till försämrad cirkulation i vävnaden.

Avhandlingen består av fem delarbeten och målet är; att utvärdera ett behandlingsprotokoll; att förbättra behandlingen i samband med svåra traumatiska skallskador; att förbättra möjligheterna till överlevnad och att minska utvecklingen av bestående skadorna; att öka förståelsen för de processer som drabbar hjärnan i samband med svåra akuta tillstånd.

I delstudie I visas att barn med svår traumatisk skallskada i åldern 0-15 år kan behandlas enligt protokollet. Behandlingen har medfört en möjlighet till överlevnad i 93 % av fallen. Långtidsuppföljning visar att 80 % av barnen har en god neurologisk återhämtning efter olyckan. Följmotmet mot behandlingsprotokollet är extremt god, ca 90 % av alla mätvärden uppnår målen i protokollet.

I delstudie II utvärderas vätskebehandlingen utifrån de angivna metodern angivna i protokollet för svår traumatisk skallskada. Resultaten visar att den dagliga mängden av vätska som patienterna får, består till 40-60 % av kolloider (en vätska med bland annat proteiner och röda blodkroppar). De första tre dygnen efter olyckan får patienterna vätska mer än normalbehovet. Med hjälp av urindrivande läkemedel, avlägsnas vätskan och balansen av vätska i kroppen återställs på dag fyra. Risken för att övriga organ i kroppen skall ta skada är ytterst liten. I ca 29 % av fallen har lungorna en risk för funktionsnedsättning under vårdperioden. I
motsvarande omfattning är lungornas funktions nedsättning väl beskriven i internationell litteratur.

I delstudie III undersöks vuxna, svårt skallskadade patienter som slumpvis delas in i grupper. De får antingen läkemedlet epoprostenol (prostacyclin) eller placebo som tillägg till behandlings protokollet. Studien värderar ämnesomsättningen i hjärnan med hjälp av en microdialysteknik och förhållandet mellan ämnena laktat och pyruvat. Detta är ett indirekt mått på cirkulation och ämnesomsättning i hjärnan. Resultaten visar att prostacyklin inte påverkar ämnesomsättningen i hjärnan i jämförelse mellan grupperna.

I delstudie IV utvärderas det inflammatoriska svaret i kroppen efter tillförsel av antingen prostacyklin eller placebo som tillägg till protokollet. Resultaten visar att tillförsel av prostacyklin sänker nivåerna signifikant av vissa inflammatoriska markörer, interleukin-6 och C-reaktivt protein (CRP), efter svår traumatisk skallskada, i jämförelse mellan grupperna. Ingen statistiskt signifikant förlagtermas överlevnad i prostacyklin gruppen jämfört med placebo kan påvisas, men dubbelt så många dör i placebo gruppen jämfört med prostacyklin gruppen.

I delstudie V analyseras ADMA hos patienter med brustet pulsåderbråck i hjärnan. Dessa patienter har en kraftig inflammatorisk reaktion och drabbas av kärl sammandragning i flera olika organ i kroppen (hjärtinfarkt, lungödem, kramp i hjärnans kärl) i samband med insjuknandet. Resultaten visar en statistiskt signifikant ökning av ADMA mängderna i blodet under veckan efter det akuta insjuknandet. Dessa nivåer kvarstår vid en tre månaders kontroll. ADMA nivåerna relaterades till ett inflammatoriskt svar med hjälp av markören CRP. Detta resultat kan vara en indikation på en kvarstående negativ kärlväggs påverkan.

Sammanfattningsvis visar studierna vid svår traumatisk skallskada hos barn och vuxna patienter en låg dödlighet och hög frekvens av gynnsamt neurologiskt utfall behandlade enligt intrakraniellt tryckstyrkt protokoll. Ett inflammatoriskt svar kan moduleras av det kroppsspegnas ämnet prostacyklin. Markören ADMA visar att kärlväggsförändringar kvarstår länge efter brustet pulsåderbråck i hjärnan.
APPENDIX - Scoring

1. **Glasgow Coma Scale (GCS)** is clinically used and has been developed for assessing the depth and duration of impaired consciousness and coma. Three aspects of behaviour are independently measured: motor responsiveness on a scale of one to six, verbal performance on a scale of one to five, and eye movement on a scale of one to four with the best responses recorded and the sum as coma grade. GCS is generally used in a wide range of diseases with impaired consciousness, apart from traumatic brain injury (Teasdale and Jennet 1974).

**The Glasgow Coma Scale**

<table>
<thead>
<tr>
<th>Motor Response</th>
<th>Verbal Response</th>
<th>Eye movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Obeying commands</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Painful stimuli</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Localising response</td>
<td>Orientation</td>
</tr>
<tr>
<td>4</td>
<td>Withdraw, flexion</td>
<td>Confused conversation</td>
</tr>
<tr>
<td>3</td>
<td>Abnormal flexion</td>
<td>Inappropriate speech</td>
</tr>
<tr>
<td></td>
<td>Extensor posturing</td>
<td>Incomprehensible sound</td>
</tr>
<tr>
<td>1</td>
<td>No response</td>
<td>Spontaneous eye opening</td>
</tr>
</tbody>
</table>

The total sum of GCS score; 3 – 15
Appendix

2. The Reaction Level Scale (RLS85) is used for assessment of overall reaction level in patients with acute brain disorders. The best response provided is recorded. Part one, RLS one to three grades the assessment of a mentally responsive patient. Part two, RLS four to eight, is an assessment of an unconscious patient. The standardised posture of the patient is laying flat on his back with the arms along the sides (Starmark, Stålhammar and Holmgren 1988).

The Reaction Level Scale

<table>
<thead>
<tr>
<th>RLS 1</th>
<th>Alert, no response delay.</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLS 2</td>
<td>Somnolent, confused, light stimulus response</td>
</tr>
<tr>
<td>RLS 3</td>
<td>Latent response to strong stimulus, very confused</td>
</tr>
<tr>
<td></td>
<td>Unconscious</td>
</tr>
<tr>
<td>RLS 4</td>
<td>Localises does not ward off pain.</td>
</tr>
<tr>
<td>RLS 5</td>
<td>Withdrawing on pain stimulus</td>
</tr>
<tr>
<td>RLS 6</td>
<td>Stereotyped flexion on pain stimulus</td>
</tr>
<tr>
<td>RLS 7</td>
<td>Stereotyped extension on pain stimulus</td>
</tr>
<tr>
<td>RLS 8</td>
<td>No response to pain stimulus</td>
</tr>
</tbody>
</table>
3. **Acute Physiologic and Chronic Health Evaluation II (APACHE II)** is a standard risk stratification scoring system within the Intensive Care Unit (ICU). It is thought to provide for case mix in clinical studies, comparison of the quality of care among ICUs, and assessment of group and individual prognoses (Wong & Knaus 1991). The most abnormal values of 12 acute physiological variables, age and chronic health status during the first 24 hours are scored. Part of the Acute Physiology Score involves a strongly associated outcome within a number of specific cardiovascular, neurological, respiratory, and gastrointestinal diagnoses. (Wagner, Knaus, Drape 1983). The APACHE prognostic scoring system was developed in 1981 as a way to measure disease severity (Knaus, et al 1981). APACHE II, introduced in 1985, was a simplified modification of the original APACHE.

### Modified Acute Physiologic and Chronic Health Evaluation II***

<table>
<thead>
<tr>
<th>Score</th>
<th>Temp°C (rectal)</th>
<th>MAP (mm Hg)</th>
<th>HR/min</th>
<th>RR/min</th>
<th>FiO₂/PaO₂ (kPa)</th>
<th>s-pH</th>
<th>S-Sodium (mmol/L)</th>
<th>S-Potassium (mmol/L)</th>
<th>Creatinine (µmol/L)</th>
<th>Hb (g/L)**</th>
<th>WBC (10E9/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>&gt; 40.9</td>
<td>&gt; 159</td>
<td>&gt; 49</td>
<td>≥ 5.0</td>
<td>&gt; 7.7</td>
<td>≥ 180</td>
<td>≥ 7</td>
<td>&gt; 600</td>
<td>≥ 180</td>
<td>≥ 40</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>39.0-40.9</td>
<td>130-159</td>
<td>140-179</td>
<td>35-49</td>
<td>4.00-4.99</td>
<td>7.60-7.69</td>
<td>160-179</td>
<td>6.0-6.9</td>
<td>300-599</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>38.5-38.9</td>
<td>110-129</td>
<td>110-139</td>
<td>2-10</td>
<td>2.10-3.99</td>
<td>7.50-7.59</td>
<td>150-154</td>
<td>5.5-5.9</td>
<td>130-179</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>38.0-38.4</td>
<td>70-109</td>
<td>70-109</td>
<td>12-24</td>
<td>&lt; 2.1</td>
<td>7.33-7.49</td>
<td>130-149</td>
<td>3.5-5.4</td>
<td>50-129</td>
<td>90-139</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>34.0-35.9</td>
<td>30-59</td>
<td>70-109</td>
<td>12-24</td>
<td>&lt; 2.1</td>
<td>7.25-7.32</td>
<td>120-129</td>
<td>2.5-2.9</td>
<td>&lt; 50</td>
<td>61-89</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>32.0-33.9</td>
<td>50-69</td>
<td>55-69</td>
<td>12-24</td>
<td>&lt; 2.1</td>
<td>7.15-7.24</td>
<td>111-119</td>
<td>2.5-2.9</td>
<td>&lt; 50</td>
<td>61-89</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30.0-31.9</td>
<td>40-54</td>
<td>70-109</td>
<td>12-24</td>
<td>&lt; 2.1</td>
<td>7.15-7.24</td>
<td>111-119</td>
<td>2.5-2.9</td>
<td>&lt; 50</td>
<td>61-89</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>&lt; 30.0-31.9</td>
<td>&lt; 50</td>
<td>&lt; 40</td>
<td>&lt; 6</td>
<td>&lt; 7.15</td>
<td>&lt; 111</td>
<td>&lt; 2.5</td>
<td>≤ 60</td>
<td>&lt; 1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>CNS***</th>
<th>Chronic Health Points</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>RLS 1</td>
<td></td>
<td>544</td>
</tr>
<tr>
<td>1</td>
<td>RLS 2</td>
<td>Elective Surgery</td>
<td>45-54</td>
</tr>
<tr>
<td>2</td>
<td>RLS 3</td>
<td>Emergency or Non Surgery ‡‡</td>
<td>65-74</td>
</tr>
<tr>
<td>3</td>
<td>RLS 4</td>
<td>≥ 75</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>RLS 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>RLS 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>RLS 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>RLS 8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† The Creatinine score is doubled for acute renal failure and
‡‡ Chronic disease with non-operative or emergency postoperative care.

Local variations of original APACHE II;
** Hb (g/L) was used instead of hematocrite (%),
*** RLS was used instead of GCS in Umeå.
Appendix

4. Sequential Organ Failure Assessment (SOFA) scores the function of six different organs on a scale from zero (no organ failure) to four (severe failure). The most abnormal data from the preceding 24 hours is scored, according to the table below. (Vincent et al. ICM 1996).

**Sequential Organ Failure Assessment**

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td>40.0–53.</td>
<td>26.7–39.9</td>
<td>13.4–26.6</td>
<td>0.0–13.3</td>
</tr>
<tr>
<td><strong>(PaO₂/FiO₂ kPa)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Haematology</strong></td>
<td>101–150</td>
<td>51–100</td>
<td>21–50</td>
<td>0–20</td>
</tr>
<tr>
<td><strong>Platelets 10E⁹/L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatic</strong></td>
<td>20–32</td>
<td>33–101</td>
<td>102–204</td>
<td>&gt;205</td>
</tr>
<tr>
<td><strong>Bilirubin µmol/L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypotension : MAP &lt;70 mmHg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>µg/kg/min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dopamin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>0.1–4.9</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dopamin &gt;0.1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Epinephrine ≤0.1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dobutamin &gt;0.1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Norepinephrine ≤0.1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Creatinine µmol/L</strong></td>
<td>110–170</td>
<td>171–299</td>
<td>300–440</td>
<td>&gt;441</td>
</tr>
<tr>
<td><strong>Diuresis mL/day</strong></td>
<td></td>
<td></td>
<td>201–499</td>
<td>0–200</td>
</tr>
<tr>
<td><strong>Central Nervous system</strong></td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>3-6</td>
</tr>
<tr>
<td><strong>GCS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. The Injury Severity Score (ISS) is a method for describing the patients burden of multiple injuries, and is used to estimate the extent of trauma in six different regions of the body to predict outcome (Greenspan J Trauma 1985) (Baker et al. 1974). The ISS is based on the Abbreviated Injury Scale (AIS) (Safety CoMAoA: Rating the severity of disuse damage.I. The abbreviated scale. JAMA 215:277-280, 1971). The AIS consists of ratings, one to five, for all sorts of injuries in six different regions of the body. The ISS score is the sum of the squares of the highest scored AIS grade from the three most severely injured body regions. Severe injury is defined as ISS ≥ 16.

**Example: Calculation of ISS score**

<table>
<thead>
<tr>
<th>ISS region</th>
<th>Injury</th>
<th>AIS grade</th>
<th>AIS²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Head/neck</td>
<td>Cerebral contusion</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>2 Face</td>
<td>Ear laceration</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3 Chest</td>
<td>Pulmonary contusion</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>4 Abdomen</td>
<td>Liver laceration</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>5 Extremities</td>
<td>Tibia fracture</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>6 External</td>
<td>Abrasions</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

The Sum of AIS² = 16 + 9 + 9 = 34 ISS

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Appendix

6. **Glasgow Outcome (GOS)** is a five-point scale and describes persisting disability after brain damage, which usually consists of both mental and physical handicaps. The mental component is often the more important in contributing to overall social disability. This is a complement to GCS in order to provide a predictive system (Jennett and Bond 1975).

<table>
<thead>
<tr>
<th>GOS</th>
<th>CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>Vegetative state, persistent</td>
</tr>
<tr>
<td>3</td>
<td>Severe disability, dependent for daily support due to mentally or physical disability</td>
</tr>
<tr>
<td>4</td>
<td>Moderate disability, independent with persistent varying degrees of deficits</td>
</tr>
<tr>
<td>5</td>
<td>Good recovery, minor physiological &amp; neurological deficits</td>
</tr>
</tbody>
</table>

7. **Hunt and Hess (H&H)** classifies patients with SAH and intracranial aneurysms according to surgical risk, as related to time of intervention in the repair of intracranial aneurysms. It is based on criteria that are graded one to five on admission with concerns of the intensity of meningeal inflammatory reaction, the severity of neurological deficit and confounding diseases. Neither age nor "site of aneurysm" is used in determining the grade of risk (Hunt & Hess 1968, J Neurosurg).

<table>
<thead>
<tr>
<th>Category</th>
<th>CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Asymptomatic or minimal headache, slight nuchal rigidity</td>
</tr>
<tr>
<td>Grade II</td>
<td>Moderate to severe headache, nuchal rigidity, no neurological insufficiency (except cranial nerve palsy)</td>
</tr>
<tr>
<td>Grade III</td>
<td>Drowsiness, confusion or mild focal deficit</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Stupor, moderate to severe hemiparesis, vegetative disturbance or early decerebrate rigidity</td>
</tr>
<tr>
<td>Grade V</td>
<td>Deep coma, decerebrate rigidity or moribund appearance</td>
</tr>
</tbody>
</table>

# Confounding diseases, for example hypertension, diabetes, severe arteriosclerosis, chronic pulmonary disease or severe angiographic verified vasospasm, result in positioning the patient in the next less favourable grade.
Appendix

8. Fischer scale is from one to four and correlates to the amount of blood on a CT-scan and the risk of vasospasm (Fischer CM, Kistler JP, Davies JM: Neurosurgery 1980)

Fischer score

<table>
<thead>
<tr>
<th>Group</th>
<th>Blood amount on CT-scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No Subarachnoid blood detected on CT</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse or vertical layers &lt; 1 mm thick, not dense enough</td>
</tr>
<tr>
<td>3</td>
<td>Localised clot and/or vertical layer ≥ 1 mm thick, dense collection of blood</td>
</tr>
<tr>
<td>4</td>
<td>Intracerebral or intraventricular clot with diffuse or no SAH #</td>
</tr>
</tbody>
</table>

# Reflux of blood into ventricles frequently indicates obstruction of CSF circulation, and is associated with high incidence of hydrocephalus.
REFERENCES


References


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References

_J Neurosurg Anesthesiol_, 7, 152-6.


References


References


References


References


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References


Moncada, S., R. Gryglewski, S. Bunting & J. Vane (1976a) A lipid peroxide inhibits the enzyme in blood vessel microsomes that generates from prostaglandin endoperoxides the substance (prostaglandin X) which prevents platelet aggregation. *Prostaglandins*, 12, 715-37.


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References


References


77


References


80
References


References


References
