On evolution of intracranial changes after severe traumatic brain injury and its impact on clinical outcome

Lukas Bobinski
痛みは避けられない。でも苦しみは自分次第だ。
Pain is inevitable. Suffering is optional

村上 春樹
Haruki Murakami
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Abstract

Severe traumatic brain injury (sTBI) is a cause of death and disability worldwide and requires treatment at specialized neuro-intensive care units (NICU) with a multimodal monitoring approach. The CT scan imaging supports the monitoring and diagnostics. The level of S100B and neuron specific enolase (NSE) reflects the severity of the injury. The therapy resistant intracranial hypertension requires decompressive craniectomy (DC). After DC, the cranium must be reconstructed to recreate the normal intracranial physiology as well as to address cosmetic issues.

The evolution of the pathological intracranial changes was analyzed in accordance with the three CT classifications: Marshall, Rotterdam and Morris-Marshall. The Rotterdam scale was best in describing the dynamics of the pathological evolution. Both the Rotterdam score and Morris-Marshall classification showed strong correlation with the clinical outcome, a finding that suggests that they could be used for prognostication. We also demonstrated a clear correlation between the CT classifications and concentrations of S100B and NSE. The results revealed a concomitant correlation between NSE and S100B and clinical outcome. We found that the interaction between the ICP, Rotterdam CT classification, and concentrations of biochemical biomarkers are all associated with DC. We found a high percentage of complications following cranioplasty. Our results call into question whether custom-made allograft should be considered the best material for cranioplasty.
It is concluded that both the Rotterdam and Morris-Marshall classification contribute to clinical evaluation of intracranial dynamics after sTBI, and might be used in combination with biochemical biomarkers for better assessment. The decision to perform DC should include a re-assessment of ICP evolution, CT scan images and concentration of the biochemical biomarkers. Furthermore, when determining whether DC treatment should be used, surgeon should also consider the risks of the following cranioplasty.
List of original papers


# Abbreviations

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<tr>
<td>APACHE II</td>
<td>Acute Physiology and Chronic Health Evaluation II</td>
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<td>ASDH</td>
<td>Acute Subdural Haematoma</td>
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<td>ATP</td>
<td>Adenosine Triphosphate</td>
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<td>AUC</td>
<td>Area Under Curve</td>
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<td>AVDO₂</td>
<td>Arterio-Venous Oxygen Difference</td>
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<td>BBB</td>
<td>Blood Brain Barrier</td>
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<td>BP</td>
<td>Blood Pressure</td>
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<td>BR</td>
<td>Bulk Release</td>
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<td>CBF</td>
<td>Cerebral Blood Flow</td>
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<td>CBV</td>
<td>Cerebral Blood Volume</td>
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<td>CMR&lt;sub&gt;glc&lt;/sub&gt;</td>
<td>Cerebral Metabolic Rate for Glucose</td>
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<td>CMRO₂</td>
<td>Cerebral Metabolic Rate for Oxygen</td>
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<td>CMS</td>
<td>Codman MicroSensor</td>
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<td>CNS</td>
<td>Central Nervous System</td>
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<td>CPP</td>
<td>Cerebral Perfusion Pressure</td>
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<td>CSF</td>
<td>Cerebro-Spinal Fluid</td>
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<td>Abbreviation</td>
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<tr>
<td>CT</td>
<td>Computer Tomography</td>
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<td>CT&lt;sub&gt;i&lt;/sub&gt;</td>
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<td>CVP</td>
<td>Central Venous Pressure</td>
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<td>DC</td>
<td>Decompressive Craniectomy</td>
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<td>DAI</td>
<td>Diffuse Axonal Injury</td>
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<td>DSR</td>
<td>Disability Rating Scale</td>
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<td>EAA</td>
<td>Excitotoxic Amino Acids</td>
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<td>EDH</td>
<td>Epidural Haematoma</td>
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<td>EML</td>
<td>Evacuated mass lesion</td>
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<td>EVD</td>
<td>External Ventricular Drainage</td>
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<td>FIM</td>
<td>Functional Independence Measurement</td>
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<td>GCS</td>
<td>Glasgow Coma Scale</td>
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<td>GODS</td>
<td>Glasgow Outcome at Discharge Scale</td>
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<td>Glasgow Outcome Scale</td>
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<td>GOSE</td>
<td>Extended Glasgow Outcome Scale</td>
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<td>HR</td>
<td>Heart Rate</td>
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<td>ICP</td>
<td>Intracranial Pressure</td>
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<td>IPH</td>
<td>Intraparenchymal Haematoma</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>ISS</td>
<td>Injury Severity Score</td>
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<td>IVH</td>
<td>Intraventricular Haemorrhage</td>
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<td>MAP</td>
<td>Mean Arterial Pressure</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>NEML</td>
<td>Non-evacuated mass lesion</td>
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<td>NICU</td>
<td>Neuro-Intensive Care Unit</td>
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<td>NOS</td>
<td>Neurological Outcome Scale</td>
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<td>NSE</td>
<td>Neuron-Specific Enolase</td>
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<td>PaO₂</td>
<td>Partial Pressure of Oxygen</td>
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<td>PRx</td>
<td>Pressure Reactivity Index</td>
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<td>PMMA</td>
<td>Polymethylmethacrylate</td>
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<td>ROC</td>
<td>Receiver Operating Characteristic</td>
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<td>RR</td>
<td>Respiration Rate</td>
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<tr>
<td>SEM</td>
<td>Standard Error of the Mean</td>
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<tr>
<td>sTBI</td>
<td>Severe Traumatic Brain Injury</td>
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<td>tSAH</td>
<td>Traumatic Subarachnoid Haemorrhage</td>
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<td>VP-shunt</td>
<td>Ventriculo-peritoneal shunt</td>
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“My dear, here we must run as fast as we can, just to stay in place. And if you wish to go anywhere you must run twice as fast as that.”

— Lewis Carroll, Alice in Wonderland
Introduction

Brain metabolism and autoregulation

Under normal physiological conditions, the human brain produces almost all of its energy by aerobically converting glucose into water (H$_2$O) and carbon dioxide (CO$_2$), resulting in 32 mol of ATP for each mol of glucose. During hypoxia, this process is replaced by a far less efficient anaerobic glycolysis, as it produces only 2 mol of ATP. The metabolic demand of the brain is much higher when compared to other organs as it receives up to 20% of total cardiac output. Under normal circumstances, the cerebral metabolic rate of oxygen (CMRO$_2$) is about 3 ml/100g/min (Kety et al., 1948, Watabe et al., 2013). The mean normal adult CBF is around 50 ml/100 g per minute (Ito et al., 2004, Ibaraki et al., 2008). However, because the brain is incapable of storing glucose and glycogen, cerebral circulation must be under constant autoregulation to meet brain’s glucose and oxygen demands (Lassen et al., 1959). This autoregulation, in a large part, is influenced by the vascular endothelium as it regulates the blood flow by releasing relaxing and contracting factors. The autoregulation can be divided into three control mechanisms:

- pressure autoregulation
- metabolic autoregulation
- carbon dioxide reactivity
Pressure autoregulation:

Poiseuille’s law implies that the flow of fluid is laminar through the cylindrical tube of constant circular cross-section, when it is substantially longer than its diameter. The same equation can be applied to cerebral circulation. To retain stable cerebral blood flow (CBF) decrease of cerebral perfusion pressure (CPP) must be counterbalanced by alterations of vessel diameter. Under physiological conditions in healthy adults, CBF can be automatically regulated in the pressure range between 50 to 150 mmHg of CPP. See Fig.1

**Figure 1**

![Autoregulation curve](image)

Fig.1 Autoregulation curve. CBF remains at a constant level in healthy brain despite fluctuations in blood pressure. Normally autoregulation maintains a constant blood flow between CPP 50 mmHg and 150 mmHg
**Metabolic autoregulation:**

Regional or global metabolic changes are followed by adequate changes in CBF. This allows the brain to maintain CBF to match its metabolic needs. CMRO\textsubscript{2} reflects cerebral metabolism and remains in constant relationship with arterio-venous difference of oxygen (AVDO\textsubscript{2}). In healthy individuals, AVDO\textsubscript{2} remains relatively constant with a baseline value of about 6.7 ml/100 ml. This level can increase up to 13 ml/100 ml to account for changing metabolic demands (Bergsneider et al., 1997). When physiological circumstances require an increased metabolic response (e.g., as a response to a fever), autoregulation provides a proportional increase in CBF; however, when physiological circumstances require decreased metabolic demands (e.g., as a response to coma or hypothermia), autoregulation provides a proportional decrease in CBF.

**Carbon dioxide reactivity:**

Changes in arterial CO\textsubscript{2} provoke vascular calibre adaptations and influence CBF. Every 1 mmHg change in PaCO\textsubscript{2} (within the normal pressure range from 20 to 60 mmHg) is followed by an adequate change in CBF. Hyperventilation leads to vasoconstriction and a decrease of CBF. On the contrary, hypoventilation leads to vasodilation and increase of CBF. Changes in CO\textsubscript{2} pressure are mediated by pH in the perivascular space (Muizelaar et al., 1988).

Blood viscosity also plays role in adaptation of CBF. Increased viscosity leads
to elevated vascular resistance. According to Poiseuille’s equation, increased blood viscosity triggers an autoregulatory response to maintain relatively constant CBF by vasodilatation or vasoconstriction (Muizelaar et al., 1986).

**Blood Brain Barrier**

The BBB is composed of endothelial cells that line the cerebral vessels packed close together and forming tight junctions between the basement membrane, neurons and neuroglia (astrocytes, pericytes and microglia).

The molecules are selectively and actively transported through BBB. The endothelial cells contain a greater concentration of mitochondria and ATP due to high-energy requirements of active transportation.

Alkaline phosphatase and γ-GTP are concentrated on the intra-luminal compartment side, whereas sodium-potassium adenosine triphosphatase (Na⁺,K⁺-ATPase) and other transporters are concentrated on the extraluminal side (Abbott et al., 2006). Glucose is transported across the BBB by high molecular mass isoform (GLUT1) glucose transporter protein placed on the luminal surface of the endothelial cells (Simpson et al., 1999, Cornford et al., 2005).

**Intracranial pressure and cerebral perfusion pressure**

Because brain tissue is encased in a skull (rigid container), fluid pushed into the skull will inevitable create intracranial pressure (ICP). The intracranial space consists of blood, brain tissue, CSF and any pathologic masses. Any increase in volume of one of these compartments must be accompanied by
an equal decrease in volume of other compartments to maintain physiologic ICP. This interplay censures a constant volume. This phenomenon was first described by George Kellie and Alexander Monro in the 19th century (Andrews et al., 2004). The Monro-Kellie doctrine states that the total volume of intracranial contents (CBV, CSF, brain parenchyma and any expansivity) is constant.

\[ ICP \approx V_{\text{tot}} = CBV + CSF + \text{brain parenchyma} + V_{\text{expansivity}} \]

The largest volume (86%) is occupied by the brain, the second largest volume (10%) is occupied by the total volume of CSF (subarachnoid space, cisterns and ventricles), and the smallest volume (4%) is occupied by the blood (Ambarki et al., 2011 and 2012). Although the brain occupies most of the intracranial volume, its compensatory mechanism is effectively available only when increase in pathological volume \( V_{\text{expansivity}} \) occurs slowly. Rapid volume expansion results in brain shift, herniation, blood vessel compression and if not reversed, death. Despite the small total volume of CSF and blood, these compartments allow much faster pressure equilibration.

Cerebral perfusion pressure (CPP) is defined as arterial inflow pressure minus ICP thus it relies on an arterio-venous pressure gradient.

\[ \text{CPP} = \text{MAP} - \text{ICP} \]
Under normal physiological circumstances, the lower limit of autoregulation is within the range of 50 to 70 mmHg of CPP (Rosner et al., 1995, Brain trauma foundation, 2007b, Grande at al., 1997).

CSF is produced with a constant rate \( I_f \) by the choroid plexuses, independent to the resistance pressure. The mean volume of intracranial CSF is 164.5 ml with a range between 62.2 and 267 ml (Tanna et al., 1991, Ambarki et al., 2010).

After formation, CSF passes through the resistive elements to be aspirated through arachnoids villi. Under physiological circumstances, the pressure gradient of the \( I_f \), resistance to outflow \( R_o \) and pressure inside dural sinus \( P_{ss} \) remains in equilibrium. The CSF must be absorbed at the same rate as it is being formed in order to maintain constant CSF flow so the CSF pressure must be equal to the sum of the pressure gradient across the absorptive element \( (I_f \times R_o) \) and the exit pressure \( P_{ss} \) (Davson et al., 1966, Marmarou et al., 1978).

\[
ICP = (I_f \times R_o) + P_{ss}
\]

In adults, the usual level of normal ICP is around 15 mmHg (Malm et al., 2011). Transient physiologic changes (such as coughing or sneezing) often produce pressures exceeding 30 mmHg, but ICP quickly returns to baseline levels.
Lundberg described three basic patterns of ICP waveform: A waves (plateau waves), B waves, and C waves (a milestone of ICP monitoring) (Lundberg et al., 1960). The “A waves” are characterized by steep increase in ICP that last for several minutes (5-10 min) and then return spontaneously to a slightly higher baseline (Castellani et al., 2009). According to Lundberg the A waves are a result of an increase in cerebrovascular blood volume due to vasodilation.

The “B waves” are elevations of ICP up to 50 mmHg oscillating under a period of 0.5 to 2 minute. When B waves are present, the increased velocity in the middle cerebral artery can be demonstrated by transcranial doppler, suggesting that B waves also can be elicited by vessel dynamics (Newell et al, 1992).

The “C waves” are similar to B waves but have more rapid sinusoidal fluctuations (5-8 waves/min). C waves have been observed in healthy individuals and are probably caused by cardiac and respiratory cycles interaction.

**Epidemiology of TBI**

Traumatic Brain Injury (TBI) is a global health problem responsible for high mortality, morbidity, and economic burden for society (Corrigan et al., 2010, Maas et al., 2008). The incidence of TBI in United States is 103 per 100,000 (Langlois et al., 2006, Coronado et al., 2012).

The cost of TBI in U.S is estimated to be between 50 to 60 billion dollars
annually (Waxweiler et al., 1995, Thruman et al., 2001). Increasing use of motorized vehicles has led to a high incidence of TBI in low- and middle-income countries, resulting in high morbidity and mortality (Krug et al., 2000, Hofman et al., 2005).

Young adults, particularly males, are generally thought to sustain TBI at a higher rate than other populations (Jacobsson et al., 2007). According to the International Mission for Prognosis and Clinical Trial (IMPACT study), road traffic incidents account for between 53% to 80% of TBI and falls account for between 12% to 30% of TBI (Butcher et al., 2007). TBI as a result of falls is increasing, particularly in elderly with high mortality due to frequent use of anticoagulants associated with intracranial haemorrhages (Dams-O’Connor et al., 1997, Susman et al., 2002, Roozenbeek et al., 2013).

The overall incidence of TBI in Europe is 235 per 100 000 (Tagliaferri et al., 2006).

Three studies from Sweden reported the incidence of TBI according to region: 354 per 100 000 in northern Sweden; 546 per 100 000 in western Sweden; and recent rapport with 156 per 100 000 (Andersson et al., 2003, Styrke et al., 2007, Pedersen et al., 2015). However, the vast majority of the TBI cases are due to mild injuries (Styrke et al., 2007). The general mortality of TBI in Scandinavia was reported highest in Finland (21.2/100 000) followed by Denmark (11.5/100 000), Norway (10.4/100 000) and Sweden (9.5/100 000) (Sundström et al., 2007).
Types of intracranial injuries

Primary injury occurs at the time of the impact due to the unavoidable direct mechanical forces. Although the injuries can be divided into diffuse and focal lesions as well as open and closed injuries, we only discuss closed injuries. In general, a focal lesion has a mortality rate higher than diffuse lesion (Povlishock et al., 1983).

Figure 2

Fig. 2. Illustrates self-perpetuating circle of secondary injuries in sTBI
Many of severely head-injured patients, who eventually deteriorate, present with a period of lucidity (Reilly et al., 1975). This phenomenon emphasizes that the primary mechanical impact is usually not responsible for complete damage of the brain resulting in death. sTBI triggers a chain reaction of complex intra- and extracellular neurochemical injuries that can quickly escalate resulting in clinical deterioration or even death. These pathological changes can present in a delayed fashion and are called “secondary insults” (Miller et al., 1982, Young et al., 1988). A schematic description of that cycle is illustrated in fig. 2.

**Diffuse Traumatic Lesions**

*Concussion*

Concussion is the most common clinical manifestation of a blunt head trauma that results in rapid functional disturbance of the CNS. Concussion is the mildest form of diffuse brain injury. It occurs due to the rotational forces causing acceleration of the head. Concussion may not be associated with loss of consciousness. Repeated concussions (e.g. as a result of boxing or tackling) often results in some degree of permanent neurological impairment (Guskiewicz et al., 2003)

*Diffuse Axonal Injury*

High velocity trauma, such as the velocities experienced in motor vehicle accidents, with violent acceleration and deceleration forces can cause Diffuse Axonal Injury (DAI). This results in stretching and shearing of the axons. On
the histological level the pathognomonic signs of DAI are swelled and disrupted axons (retraction balls). Small haemorrhages are founded in the white matter (e.g. in the corpus callosum, fornix, basal ganglia, brainstem and superior cerebellar peduncles). Deep location of haemorrhages has been described as an important determinant of functional recovery (Adams et al., 1989). In patients, who are severely impaired, despite lack of gross parenchymal changes visible at computer tomography scan (CT), DAI needs to be suspected. These patients need to be evaluated using magnetic resonance imaging (MRI). The haemorrhagic lesions after DAI can be visualized using T2-weighted gradient-echo magnetic resonance investigation (MRI-GE). The shearing injuries are better assessed by diffusion-weighted (DW) sequences (Ezaki et al., 2006).

The investigation of DAI effects using animal models revealed astrogial and neuroinflammatory responses (Ekmark-Lewén et al., 2013). This finding suggests that TBI initiates the injury of axons by mechanical shearing forces but the degradation of the distal part of axons continues due to biochemical inflammatory response.

**Focal Traumatic Lesions**

Focal brain damage is a direct result of the mechanical insult delivered at the time of injury. The focal primary brain injury lesions often evolve over time (Sahuquillo et al., 2001).

*Skull fracture*
The severity of skull fracture indicates the destructive energy transmitted to the skull and the brain during the impact. These fractures also indicate possible types of brain injuries: contusions of the brain cortex, vascular injuries that can lead to extra-axial haematomas and dural tears that can increase the risk for infection. 50% of patients with severe TBI and skull fracture present with intracranial haematoma on initial CT scan (Miller et al., 1986).

**Contusions**

Contusions occur due to impact of the brain against the rigid intracranial structures like dural edges and inner skull bone. Because the brain is loosely anchored within the cranial cavity, sudden acceleration/deceleration of the head can force the brain to move substantially within the skull. Movement of the brain forward results in contusions of inferior surface of the frontal lobes and the tips of the temporal lobes (Lu et al., 2005). This leads to injury of small blood vessels (e.g. capillaries, veins and arteries) and other tissue components (i.e. nerve and glial cells) of the neural parenchyma. Contusions are a source of secondary injury through release of neurotransmitters and focal changes due to impaired autoregulation, cerebral swelling and ischemia (McHugh et al., 2007, Nortje et al., 2004, Katayama et al., 1990). About 30% of the patients with sTBI present with contusions on initial CT scan (Lobato et al., 1983). These are dynamic lesions that usually increase in size and can transform into intraparenchymal haematomas (IPH). These can be a life-threatening due to the mass-effect with subsequent ICP elevation and can be responsible for rapid neurological deterioration after a lucid interval.
Intraparenchymal Haematoma

IPH can be seen as a primary lesion in patients with severe closed head injuries (Soloniuk et al., 1986). They are usually associated with skull fractures and extensive lobar contusions. IPHs often arise from cerebral contusions and similarly occur in the orbitofrontal and temporal lobes (Rivano et al., 1980) so it is often difficult to distinguish IPH from cerebral contusions (Zimmerman et al., 1978). Moreover, IPHs are also progressive lesions and can increase in size during the first 24 hours (Narayan et al., 2008, Oertel et al., 2002, Chang et al., 2006). This is usually the cause of rapid deterioration after a lucid interval. Almost half of the patients with IPH can die or become severely disabled if not treated at a NICU (Lobato et al., 1991). Patients on anticoagulation and antiplatelet therapy are at an increased risk for developing IPH, even after mild head injury (Baratham et al., 1972).

Epidural Haematoma

EDH is characterized by a biconvex, hyperdense blood collection visible on a CT scan. Only 2% of TBI patients admitted to the hospital presents with EDH (Maloney et al., 1969). EDHs typically occur in patients younger than 50 years, although they can be present in all age groups (Heiskanen et al., 1975). Typical localization of EDH is above temporo-parietal area due to
injury of the middle meningeal arteries and veins, but it can also be seen parasagittally as well as in anterior and posterior fossa (Jamieson et al., 1968). Sometimes EDH, as a result of skull fracture can be of a venous origin due to tearing of venous dural sinuses, emissary veins or bone (Yilmazlar et al., 2005).

The classic clinical course of a patient with EDH presents with initial loss of consciousness after trauma, transient complete recovery (“lucid interval”) followed by a rapid progression of neurological deterioration with hemiparesis, decreased level of consciousness and ipsilateral oculomotor nerve palsy (Gallagher et al., 1968, Reale et al., 1984). Patients with pure EDHs can have an excellent prognosis if pathology is recognized in time and treated with surgical evacuation. However, non-recognized haematoma can lead to decerebrate rigidity, respiratory disturbances, and finally, apnea and death due to its further expansion.

Acute Subdural Haematoma

ASDH, most common focal intracranial lesion in sTBI, occurs after a brief, rapid deceleration movement that tears parasagittal bridging veins causing haemorrhage between dura and arachnoid surface (Gennarelli et al., 1982). In higher velocity traumas, the source of the ASDH can be other structures adjacent to the subdural space, such as injured superficial cortical vessels or contusions and IPH that expand into subdural space through injured cortex (Jamieson et al., 1972). Most common sites are the temporal and/or frontal lobes. ASDHs are threatening lesions because the compressive effects
(elevated ICP) can trigger secondary insults (cerebral ischemia) due to impaired cerebral perfusion (Graham et al, 1989, Miller et al., 1990). Early surgical evacuation of the haematoma significantly improves neurological outcome (Wilberger et al., 1991). Nevertheless, patients have extremely poor prognosis if initial CT scan demonstrate large ASDH with accompanying brain swelling and low initial GCS (Sawauchi et al., 2008).

**Traumatic Subarachnoid Haemorrhage**

The improved methods of diagnostics (modern CT scanners with high resolution) have resulted in higher frequency of detected tSAH (Greene et al., 1995, Mattioli et al., 2003). tSAH may be considered as a marker of adverse outcome due to extensive injuries of cerebral tissue (Taneda et al., 1996, Kakarieka et al., 1994). However, tSAH by itself can directly influence outcome via secondary insults such as inflammation, cerebral ischemia, hydrocephalus and post-traumatic vasospasm similar to aneurysmal SAH (Grolimund et al., 1988, Oertel et al., 2005). Post-traumatic vasospasm is an independent predictor of neurological deficit and poor outcome (Lee et al., 1997, Chieregato et al., 2005). Anterior circulation is specifically amenable toward vasospasm (Martin et al., 1994, Romner et al., 1996). Posterior circulation can also be a site of post-traumatic vasospasm but is much less frequent (Marshall et al., 1978, Soustiel et al., 2004).

**Injury on cellular level**

Haemorrhagic mass lesions, vascular injuries and contusions of the cerebral parenchyma compromise the microcirculation. Moreover, due to impaired
autoregulation, increasing ICP further reduces blood flow (Schroder et al., 1995, Graham et al., 1985). This impairment initiates a cascade of intra- and extracellular changes compromising the integrity of cell membranes, ion channels and mitochondrial function altering brain metabolism and blood-flow, causing dysfunction of neurons and astrocytes (Gaetz et al., 2004).

sTBI patients are extremely vulnerable for ischemic brain damage that can lead to cell necrosis and further toxic injury by a negative feedback loop (Gennarelli et al., 1993). Hypoxia and ischemia, essential factors involved in secondary insults after sTBI, are defined by a blood flow below 12 ml/100 g/min (Young et al., 1988, Siesjö et al., 1992). This blood flow level induces anaerobic metabolism, a process that is unable to keep up with ATP requirements. This energy depletion results in depolarization of the cell membrane due to ATP dependent sodium-potassium pump (Na+, K+-ATPase). Following sodium influx, through α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, activation of the Na+/H+ and Cl-/HCO3- exchangers allows water to passively enter the cell (Jones et al., 1981, Zonta et al., 2003, Volterra et al., 2005). Simultaneously, cells leak the potassium ions and excitotoxic amino acids (EAA) into the extracellular space.

At this stage astrocytes are incapable of maintaining the clearance of the EAA (i.e., glutamate) from extracellular space, re-inforcing the process of cytotoxic oedema by their connection to N-methyl-D-aspartate (NMDA) receptors (Kaku et al., 1993). This glutamate-driven toxic chain-reaction spreads across the cerebral tissue with further cell depolarization, oedema
and cell injury. All these processes are linked and self-perpetuating and are responsible for delayed neuronal degeneration due to apoptosis and necrosis (Tsujimoto et al., 2006, Wang et al., 2000, Kampfl et al., 1997, Wyllie et al., 1980). The activation of NMDA causes an intracellular increase of Ca$^{2+}$ (Choi et al., 1995, Shapira et al., 1989), activating destructive enzymes (phospholipases, calpain, caspase, and nitric oxide synthase [NOS]), releasing free radicals that damage and inhibit the function of all components of the cell, including proteins, nucleic acids and lipids (Zipfel et al., 2000, Wang et al., 2000, Pun et al., 2009). Furthermore, Ca$^{2+}$ causes calcium-induced process of increased mitochondrial membrane permeability that leads to mitochondrial dysfunction and by deficiencies in neuronal metabolism and ionic equilibrium resulting in the death of cells (Hunter et al., 1979).

**Pathological evolution of brain oedema**

Previous studies suggest that cerebrovascular reactivity and autoregulation remains intact during the first 36 hours but becomes abnormal or even absent in up to 50% of patients between 36 and 96 hours after sTBI (Fieschi et al., 1974). However, more recent findings suggest an early deterioration of cerebrovascular reactivity and autoregulation (Czosnyka et al., 2008). Pressure autoregulation can become unstable as a result of endothelial damage (Wei et al., 1980). This damage can be caused by oxygen radicals generated after injury due to mitochondrial failure (Beckman et al., 1990). This compromises normal oxidative metabolism and shifts cells toward the anaerobic glycolytic pathway, which is insufficient to maintain energy
requirements even if CMRO$_2$ decreases from a normal value of 3.2 ml/100 g per minute to 2.3 ml/100 g per minute (Sunami et al., 1989, Andersen et al., 1992, Marmarou et al., 1993, Bergsneider et al., 1997). Despite lower energy requirements patients might present with CBF that exceeds CMRO$_2$ requirements because of impaired autoregulation. This phenomenon, called hyperaemia is prevalent between one and five days after TBI and is strongly associated with diffuse cerebral swelling and elevated ICP (Lassen et al., 1966, Marion et al., 1991).

Around 50% of the patients with elevated ICP have underlying intracranial mass lesions in comparison to only 33% of those with diffuse injuries (Becker et al., 1977). ICP above 20 mmHg is a significant independent determinant of outcome (Miller at al., 1977, Schreiber et al., 2002), however, it has been suggested that the ICP thresholds can be individualized by using continuous monitoring of PRx (Lazaridis et al., 2016). On the contrary, adjusted ICP monitoring with controlled low ICP correlates to significantly better outcome after sTBI (Saul et al., 1982, Yuan et al., 2016).

In physiological setting, an intracranial volume of 26±4 ml increases ICP from 1 to 10 mmHg. However, it requires only 6.4 ml to further increase ICP from 10 to 20 mmHg (Shapiro et al., 1980). This relationship between intracranial volume and ICP can be described by a hyperbolic curve, the so-called pressure-volume curve. Along the plateau of the curve, increase in volume is only associated with minimally ICP change due to compensatory mechanisms. However, a further increase in volume, results in the increasingly large pressure change per unit, and lower compliance. When the
pressure exceeds 50 mmHg of the ICP, the curve tends to flatten again. The complete curve has a more sigmoid form (Cloots et al., 2008) as shown in fig. 3.

**Figure 3**

Fig.3. *ICP pressure-volume curve. Compensation phase (1 and 2)-ICP remains almost constant with increase of intracranial volume. Decompensation phase (3 and 4)-increase of intracranial volume causes rapid escalation of ICP.*

Elevated ICP may be compensated by translocation of CSF and venous blood from the intracranial vault, but at a certain point this volume-buffering capacity is exhausted, and an exponential pressure rise occurs with further increase in volume (Marmarou et al., 1978). The change in pressure in relation to volume is represented by compliance or tightness of the brain. This change can be estimated either by injecting or withdrawing small
quantities of fluid into or from the CSF space with simultaneous recording of ICP or by analyzing the slope and amplitude of the ICP pressure wave (Czosnyka et al., 1994, 1996). The RAP index (amplitude-pressure regression) is calculated as a linear correlation coefficient between the ICP pulse amplitude and mean ICP, possibly reflecting the intracranial compensatory reserve. RAP index of zero denotes the compliant intracranial space (flat part of the pressure-volume curve) where the change of volume produces no or very little change in pressure. A rising RAP index demonstrates deterioration of intracranial compliance (steep part of the pressure-volume curve). When RAP index reaches +1, the pulse amplitude varies directly with ICP and therefore any further increase in volume triggers rapid ICP elevation. Additional increase in volume leads to complete loss of compliance and brain herniation (flattened part of the pressure-volume curve) as demonstrated by a decrease in pulse amplitude and RAP index falling below “0” (Czosnyka et al., 2004, 2007).

Raised ICP causes headache and vomiting. Papilloedema is not a reliable objective measure of acutely raised ICP. Continuous ICP elevation may cause a various degrees of cranial nerve palsies as a result of pressure effect on the brainstem nuclei or directly on the nerves. If ICP increases beyond compensation capabilities, the patient becomes comatose and arterial hypertension, bradycardia and abnormal respiration (Cheyne-Stokes respiration pattern) may be exhibited, the so-called Cushing response.
Types of Cerebral Oedema

The self-perpetuating loop of pathologic events leads to cerebral oedema, which is an accumulation of fluid in the intracellular and/or extracellular space. This accumulation occurs in almost all patients with sTBI, but only in minority of those with minor and moderate injuries.

sTBI induced cerebral oedema can be divided into two distinctive forms:

- Cytotoxic: as a result of metabolic failure with influx of ions and water and cellular swelling of all cerebral tissue elements (neurons, glial, and endothelial cells)

- Vasogenic: as a result of injury of the BBB vascular permeability increases so there is extracellular fluid accumulation

Historically, vasogenic oedema was believed to be the primary component of the cerebral oedema after TBI (Kuroiwa et al., 1985). However, vasogenic oedema represents only about 25% of TBI cases, whereas the majority of cerebral swelling is due to cytotoxic oedema as confirmed by diffusion-weighted MRI (Ito et al., 1996, Marmarou et al., 2006 and 2007).

Prevention of secondary insults

The main goal of pre-hospital and in-hospital care is preventing an occurrence of secondary insults, specifically hypotension, hypoxemia, hyperglycaemia, and hyperthermia.
One of the most fearsome complications with direct impact on outcome after TBI is hypotension (Butcher et al., 2007). Even a single episode of hypotension after TBI increases morbidity and doubles mortality (Chesnut et al., 1993, Manley et al., 2001). Unfortunately, up to 20% of TBI patients will present with at least one episode of hypotension (McHugh et al., 2007). Therefore, a management protocol that prevents hypotension is recommended at initial resuscitation. Current recommendation is to maintain systemic blood pressure (SBP) above 90 mmHg after TBI (Brain Trauma Foundation et al., 2007b). However, different reports from the IMPACT database suggest that the threshold should be even higher (Finfer et al., 2004).

Hypoxemia also contributes to poor outcome. Both pre- and in-hospital desaturation episodes have been reported to increase mortality and to result in poor neurological outcome (Stocchetti et al., 1996, Chi et al., 2006). The current recommendation is to maintain oxygen saturation above 90% and PaO₂ at 12 kPa (Brain Trauma Foundation et al., 2007b). However, the impact of hypoxia and hypotension episodes on long-term outcome during pre-hospital resuscitation varies in the literature. Brorsson et al., demonstrated no significant difference in long-term outcome between patients with sTBI with and without hypoxia and hypotension episodes. Furthermore, there was no significant difference in outcome between patients transferred directly to a level 1 trauma centre and patients transported first to primary hospital (Brorsson et al., 2011).
Hyperglycaemia is another avoidable secondary insult, which correlates with worse neurological outcome due to increased anaerobic metabolism and amplified lactic acidosis (De Salles et al., 1987, Young et al., 1989, Marmarou et al., 1993).

In addition, hyperthermia after TBI may lead to an increased cerebral metabolism. In case of injured autoregulation, hyperthermia can be a source of additional ischemic changes due to a compromised microcirculation (Dietrich et al., 1992, Chatzipanteli et al., 2000, Elf et al., 2008). This condition might be especially dangerous and evident due to anaemia, further impeding the cerebral haemoglobin-bound oxygen supply. A recent report from the IMPACT group confirms that anaemia correlates with worse outcome. However, the optimal haemoglobin level remains unknown (Van Beek et al., 2007).

**Diagnostics**

As evident in the discussion above it is crucial that these patients are resuscitated and provided with medical stabilization and radiologic diagnosis as soon as possible. This should be followed by aggressive surgical and medical treatment of intracranial mass lesions, raised ICP and decreased CPP, if required (Brain Trauma Foundation et al., 2007a).

The clinical status of the patients after sTBI as well as severity of the injury can be evaluated using the Glasgow Coma Scale (GCS). Presented in 1974 by Teasdale and Jennet, it is the most known and used TBI classification (Teasdale et al., 1974). The GCS consists of the sum score (range 3 to 15) of
three components: eye opening responses (1-4); verbal responses (1-5); and motor responses (1-6). On the basis of the GCS cumulative results, TBI can be classified as mild (GCS 15-14), moderate (GCS 13-9), or severe (GCS 8-3). The examination of motor component is most reliable in patients with sTBI, whereas the eye and verbal responses are more useful in patients with moderate and mild TBI. GCS motor score together with age, pupil response and CT characteristics are the most powerful independent variables of prognosis according to the IMPACT (Marmarou et al., 2007, Teasdale et al., 2014). However, the utility of GCS is somewhat limited in the modern therapeutic setting. As mentioned above, it is crucial to control systemic blood pressure and oxygenation of the patients after sTBI. Therefore upon the arrival to the hospital, patients are usually sedated and intubated, as they are unresponsive because of neuromuscular medical relaxation. An accurate re-evaluation score at admittance to the hospital cannot be determined in these patients until pharmacologic agents are actively antagonized or metabolized. Similar challenges are faced during management at NICU after initiation of ICP-lowering medical therapy. Moreover, wake-up test during which patients are still intubated but sedation is withdrawn, may lead to unnecessary increase of ICP, CPP as well as release of stress hormones (Skoglund et al., 2012 and 2014). Many of the sTBI patients are multi-traumatized. Examination of the patients with extracranial injuries like cranio-facial lacerations and swelling, limb fractures and traumatic amputations as well as chest/abdominal injuries can be very painful and exhausting. It has been reported that these confounding variables contribute to inaccurate GCS score calculations (Bledsoe et al., 2015). Stein et al., have
developed an alternative classification for severity of injury based on GCS assessment using clinical information regarding loss of consciousness (Stein et al., 1995).

Computer Tomography scanning
The first classification system for assessment of head injury based on initial CT scan findings was proposed in 1991 by the National Institutes of Health (NIH) Trauma Coma Data Bank (TCDB). The classification called the “Marshall score” was created to predict outcome based on initial radiographic criteria (Marshall et al., 1991). The Marshall classification is summarized in Table 1. It divides pathological findings into two groups: diffuse injuries (Marshall I-IV) and focal lesions (Evacuated mass lesion and Non-evacuated mass lesions). However, this classification has some drawbacks: it ignores the fact that in most cases patients present with both focal and diffuse injuries and ignores the tSAH, which has been shown to be a very important prognostic factor, can be presented in up to 60% of initial scans (Greene et al., 1995, Chiregato et al., 2005).

The first classification of tSAH was proposed by Morris and Marshall in 1997 (Morris et al., 1997). The details are presented in Table 2.
<table>
<thead>
<tr>
<th>Table 1: Marshall CT classification of TBI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diffuse injury I</strong></td>
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<tr>
<td><strong>Diffuse injury II</strong></td>
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<tr>
<td></td>
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<tr>
<td><strong>Diffuse injury III</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Diffuse injury IV</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Evacuated mass lesion (EML)</strong></td>
</tr>
<tr>
<td><strong>Non evacuated mass lesion (NEML)</strong></td>
</tr>
<tr>
<td><strong>Brain dead (BD)</strong></td>
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<td></td>
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<tr>
<td></td>
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<td></td>
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</tbody>
</table>
Table 2

<table>
<thead>
<tr>
<th>Grade</th>
<th>CT Scan Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No CT evidence of traumatic subarachnoid haemorrhage (tSAH)</td>
</tr>
<tr>
<td>1</td>
<td>tSAH present only in one location</td>
</tr>
<tr>
<td>2</td>
<td>tSAH present at only one location, but quantity of blood fills that structure OR tSAH is at any two sites, filling neither of them</td>
</tr>
<tr>
<td>3</td>
<td>tSAH present at two sites, including the tentorium filled with blood</td>
</tr>
<tr>
<td>4</td>
<td>tSAH present at 3 or more sites, any quantity</td>
</tr>
</tbody>
</table>

*Table 2: Morris-Marshall CT classification of tSAH*

Recently an “upgraded” version of the Marshall classification was proposed (Maas et al., 2005). This classification recognized as the Rotterdam score, accounts for additional radiographic criteria (tSAH) and presents the score as a mathematical sum of all pathological changes seen at CT scan. Therefore, this classification allows for an easy re-assessment regardless of time or surgical intervention. The Rotterdam score has been shown to substantially enhance the outcome prediction (Maas et al., 2007). The details of Rotterdam classification are summarized in Table 3.
Table 3

<table>
<thead>
<tr>
<th>Biomarkers of CN injury</th>
<th>Rotterdam classification score chart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cisterns</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Compressed</td>
<td>1</td>
</tr>
<tr>
<td>Absent</td>
<td>2</td>
</tr>
<tr>
<td>Midline shift</td>
<td></td>
</tr>
<tr>
<td>No shift or shift &lt;5 mm</td>
<td>0</td>
</tr>
<tr>
<td>Shift &gt;5 mm</td>
<td>1</td>
</tr>
<tr>
<td>Epidural mass lesion</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>0</td>
</tr>
<tr>
<td>Absent</td>
<td>1</td>
</tr>
<tr>
<td>Intraventricular blood or tSAH</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
</tbody>
</table>

Sum score + 1

*Add plus 1 to make the grading numerically consistent with the grading of the motor score of the GCS and with the Marshall CT classification.

Biomarkers of CNS injury

Biochemical biomarkers of cerebral injury are molecules released from the CNS that can be measured and quantified in CSF or peripheral blood after TBI. S100B and neuron-specific enolase (NSE) have been validated as markers of tissue damage in the CNS (Persson et al., 1987, Ingebrigtsen et al., 1997).
The S100 family consists of more than 15 different proteins and was initially isolated from bovine brain (Moore et al., 1965, Zimmer et al., 1995). S100B has been extensively investigated as a specific CNS injury marker (Ingebrigtsen et al., 2003, Unden et al., 2007, Donato et al., 2013). It is an intracellular, calcium-binding protein unique in its predominant location both in astrocyte and Schwann cells (Haimoto et al., 1987, Reiber et al., 1998, Mercier et al., 2000). S100B can also be found in various other cells: e.g., macrophages, melanocytes, adipocytes, chondrocytes, Langerhans cells, dendritic cells and keratinocytes (Steiner et al., 2007, Donato et al., 2003). It has a wide spectrum of functions on the cellular level (e.g., astrocytosis and axonal proliferation, neuro-protective properties, Ca\(^{2+}\) homeostasis, and regulation of allergy and the inflammatory response) (Lesniak et al., 2009, Donato et al., 2013). sTBI leads to disruption of BBB causing a leakage of proteins and vasogenic brain oedema (Marmarou et al., 2003). Because S100B is suspected to continuously be released after the sTBI either through disrupted BBB or active secretion (Gerlach et al., 2006, Plog et al., 2015), it has been proposed as a marker for BBB permeability (Marchi et al., 2003, Lopez et al., 2012). Various half-lives from 25 to 100 minutes have been reported for S100B (Blomquist et al., 1997, Ingebrigtsen et al., 2003) and eventually it is entirely eliminated by the kidneys (Usui et al., 1989). Normal serum value of S100B is <0.05 µg/l. S100B, however, also has an extra-cerebral source of secretion (Anderson et al., 2001). Extra-cranial injury source is usually responsible for much lower concentration of S100B (up to
0.57 µg/l) compared to TBI with a concentration up to 4.01 µg/l (Herrmann et al., 2000, Stalnacke et al., 2006). In CT studies, S100B has been demonstrated to have a negative predictive value of 0.99 for detecting intracranial pathology after mild TBI (Ingebrigtsen et al., 1999 and 2000).

**Neuron-Specific Enolase**

The second most recognized and validated biomarker of TBI is NSE (Pleines et al., 2001), an isoenzyme of the glycolytic enolase (2-phospho-D-glycerate hydrolase), a soluble protein released by neurons and neuroendocrine cells (Marangos et al., 1987). NSE’s normal values are <10 µg/l (Nygaard et al., 1998). Because different tumours of neuronal origin can also produce NSE, NSE has been established as a diagnostic and prognostic serum marker in the clinical management of neoplasms (Carney et al., 1982, Fizazi et al., 1998). NSE has a very long half-life, around 20 to 30 hours (Johnsson et al., 2000). Because NSE is found in erythrocytes, haemolysis might produce a false positive NSE levels, limiting NSE usefulness as a biomarker (Schmitt et al., 1998).

**Treatment**

The protocol driven treatment of TBI at NICU has been shown to improve the outcome (Elf et al., 2002, Patel et al., 2002). In United States the first protocol for treatment of TBI was presented by Rosner and Doughton and was called “CPP targeted therapy” (Rosner et al., 1995). In 1996, the Brain Trauma Foundation in co-operation with American Association of Neurological Surgeons, and the Congress of Neurological Surgeons
(AANS/CNS) published “Guidelines for the Management of Severe Traumatic Brain Injury” (Bullock et al., 1996). The latest, updated evidence-based guidelines, were released in 2007 by the Brain Trauma Foundation at AANS/CNS Joint Section on Neurotrauma and Critical Care (Brain Trauma Foundation et al., 2007a, 2007b, 2007c).

European guidelines for TBI therapy were presented in 1997 by the European Brain Injury Consortium (Maas et al., 1997). In Japan the treatment guidelines were presented by the Japan Society of Neurotraumatology (JSNT) (Shima et al., 2010). In the 1994, Asgeirsson, et al. presented ICP targeted therapy guidelines (the “Lund concept”), an approach that focused on the haemodynamic principles of volume regulation in the brain after TBI (Asgeirsson, et al. 1994).

Around that time, this treatment protocol was adopted by the Department of Neurosurgery at Umeå University Hospital (Grände, et al. 1997a; Grände, et al. 1997b, Koskinen et al., 2014). A number of publications reported very promising results of low mortality and high percentage of favourable outcomes in patients with sTBI treated according to this protocol (Eker, et al. 1998, Naredi, et al. 2001, Wahlström, et al. 2005). The goal of the protocol is to control the ICP by reduction of brain metabolism with sedation, elimination of stress, normalization of the capillary hydrostatic pressure and the fluid balance, and prevention of reperfusion hyperaemia without depleting CBF. The principles are summarized in table nr 4.
Table 4: The summarized guidelines of ICP targeted therapy based on the “Lund concept” (Olivecrona et. al., 2007)

Further, it is of outmost importance to surgically remove mass lesions in order to decompress the brain, regain normal ICP and thus secondary restore the micro-circulation of the brain.

All patients with GCS≤ 8 have to be suspected for sTBI. The initial
management should follow the ATLS® guidelines (Advanced Trauma Life Support®, American College of Surgeons). Early sedation and intubation are advocated. The patients are medically stabilized at the accident scene followed by early transportation to the nearest medical facility for damage control, clinical stabilization and radiologic diagnostics with trauma CT scan (including the brain). Unconscious patients with brain injury as well as multi-traumatized patients who require complex treatment are then transported to a hospital with neurosurgical service. It has been reported that patient who sustained TBI have much lower mortality when treated in collaboration with neurosurgical service (Patel et al., 2005). In modern neurointensive settings, the outcome after sTBI largely depends on early diagnostics, stabilization of the patients, and surgical evacuation of space occupying mass lesions. It is essential that medical and surgical treatment are followed by careful monitoring and diagnostics to identify, prevent, and aggressively treat any secondary insults that will impair ultimate recovery. Modern intensive care management simply attempts to provide the brain an optimal environment to recover. Thus, a well-defined treatment protocol should be used at neuro-intensive care units. The therapeutic goal is to maintain ICP below 20 mmHg. In order to prevent secondary ischemic brain injury, it is mandatory that CPP >50 mmHg (Nordström, et al. 2003). At our unit, all unconscious patients are sedated with midazolam and fentanyl, intubated, and mechanically ventilated at NICU. We surgically remove all space occupying mass lesions (EDH, ASDH, and IPH) discovered on initial CT scan that cause elevated ICP.
Normoventilation is mandatory (PaO$_2$ ≥ 12 kPa, Saturation >90%, PaCO$_2$ 4.5-5.5 kPa). Caution is taken to prevent hypoxia. Hyperventilation is only allowed as a temporary rescue procedure, in order to decrease ICP before surgical intervention. Multimodal monitoring is applied. The arterial blood pressure is monitored continuously with the reference at the heart level. A standard monitoring device is used to calculate both mean arterial blood pressure (MAP) and cerebral perfusion pressure (CPP). If MAP allows, metoprolol (β₁-antagonist) and clonidine (α₂-agonist) can be introduced to reduce sympathetically mediated stress and sustain normotension. Infusions of packed red blood cells (Hb > 110 g/l), albumin (S-alb > 40 g/l), Ringer's acetate and glucose solutions are used to maintain normovolemia and normal oncotic pressure. It is essential to maintain normal sodium levels (135 - 150 mmol/l). Hyperglycaemia or hypoglycemia is not allowed. Blood glucose is kept within normal values (4 – 8 mmol/l) and hypothermia is not applied. If low dose thiopental needs to be administered (ICP > 20 mmHg despite sedation), cEEG is also applied. Delta activity is the goal and burst suppression is not allowed. No initial head elevation is applied.

According to the protocol all patients with TBI and GCS ≤ 8 have to receive an ICP measuring device. As a first choice we use an intraparenchymal Codman MicroSensor™ (CMS). CMS has been shown to have few complications and be very reliable (Koskinen et al., 2005, 2013). The measurement of ICP by an EVD technique is probably the cheapest and most popular method of measuring the ICP. However, the estimated complication rate is higher in comparison to CMS. Haemorrhagic complications occur in
less than 2% of cases, but infections occur in 10% of cases (Davis et al., 2004, Lozier et al., 2008). Furthermore, the EVD is susceptible to technical malfunction due to misplacement and clogging.

The decision flow chart is described in fig.4.

**Barbiturate (Thiopental)**

Barbiturates can effectively decrease medical and surgical refractory ICP by altering vascular tone, reducing CMRO₂, and coupling with CBF to improve regional metabolic demands (Smith et al., 1972). Lesser CBF that ensues from barbiturate administration results in decreased CBV and ICP (Ward et al., 1985). However, barbiturates can have an adverse effect on outcome (Schwartz et al., 1984), due to the associated risk for systemic complications such as hypotension, myocardial depression, infections, hepatic dysfunction, skin breakdown and renal failure (Schalen et al., 1992, Schirmer-Mikalsen et al., 2007).
Figure 4

Vaspressors are commonly required to maintain therapeutic MAP and CPP. The infusion needs to be maintained for several days until stabilization of ICP. Therefore, barbiturates should not be used as prophylactic therapy. Their use should be reserved for haemodynamically stable patients with elevated, refractory ICP. cEEG is used to evaluate the response to thiopental infusion. The goal is to monitor delta activity and prevent occurrence of a burst-suppression (Winer et al., 1991).
Decompressive Cranieotomy

Introduced at the beginning of 20th century by Kocher and Cushing (Kocher et al., 1901, Cushing et al., 1905), DC increases space for the brain, reversing the impact of increased ICP on cerebral circulation. This increase in space can be achieved by elevating a part of the cranium (temporal, frontal, and occipital). The area of decompression has to cover approximately 12 x 8 cm (at least) since the size is directly associated with ICP reduction (Aarabi et al., 2006, Skoglund et al., 2006). The dura opening is an essential part of this procedure as it further reduces ICP from 30% to 85% (Jourdan et al., 1993). DC has an immediate effect on elevated ICP (Hutchinson, et al. 2006; Olivecrona et al., 2007, Timofeev et al., 2006, Cooper et al., 2011, Walcott et al., 2012); however, its role in treatment of sTBI and in the control of intracranial hypertension remains a matter of debate (Schirmer et al., 2008, Cooper et al., 2011).

DC is commonly used tactic in many centres specializing in the management of TBI. DC is also used in the Umeå ICP targeted therapy protocol as a last step in treatment of refractory intracranial hypertension.

Prostacyclin

PGI2, discovered by John Vane and first reported by Moncada et al. (1976), is a highly effective vasodilator produced in endothelial cells that line the vascular walls. PGI2 inhibits platelet activation and their aggregation (a part of blood clot formation) and remains in equilibrium with the thromboxane (TXA2) as a part of cardiovascular homeostasis. In case of trauma, this balance can be shifted towards TXA2 (Gryglewski et al., 1978, Vane et al., 2003). Experimental studies on the effects of traumatic brain injury suggest
that PGI₂ may have valuable effects not only on microcirculation but also on the permeability of the capillary system (Möller et al., 1997, Bentzer et al., 2001). PGI₂ could be an option in patients with TBI (Grände et al. 2000).

However, the results of randomized placebo controlled trial on the effect of PGI₂ in treatment of sTBI do not support this theory in a clinical setting (Olivecrona et al., 2009).

**Outcome**

The International Data Bank (IDT) started in the 1970s as an effort to create a multicentre study of the management of TBI. The result of this international research project was the development of the Glasgow Outcome Scale (GOS) reported in 1975 by Jennett and Bond (Jennett et al, 1975). The details of GOS are summarized in table 5.

**Table 5**

<table>
<thead>
<tr>
<th>Glasgow Outcome Scale (GOS)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Dead)</td>
<td>Unresponsive for period of time before death</td>
</tr>
<tr>
<td>2 Persistent vegetative state</td>
<td>Unresponsive for period of time before death</td>
</tr>
<tr>
<td>3 (severe disabled)</td>
<td>Dependent for daily support 24 hours a day</td>
</tr>
<tr>
<td>4 (Moderate disabled)</td>
<td>Able to use public transportation and work in sheltered environment</td>
</tr>
<tr>
<td>5 (Good recovery)</td>
<td>Resumption of normal life; there may be minor neurological or/and psychological deficits</td>
</tr>
</tbody>
</table>

Table 5. *The summary of Glasgow Outcome Scale (Jennett et al., 1975)*
In 1998 Wilson et al. proposed an Extended Glasgow Outcome Scale (GOSE) as a more detailed version of GOS (Wilson et al., 1998). The GOSE is summarized in table nr. 6.

**Table 6**

<table>
<thead>
<tr>
<th>Extended Glasgow Outcome Scale (GOSE)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>1</td>
</tr>
<tr>
<td>Vegetative state (Unresponsive)</td>
<td>2</td>
</tr>
<tr>
<td>Severe disability (Completely dependent 24/7)</td>
<td>Lower severe disability</td>
</tr>
<tr>
<td></td>
<td>Upper severe disability</td>
</tr>
<tr>
<td>Moderate disability (Independent but disabled)</td>
<td>Lower moderate disability</td>
</tr>
<tr>
<td></td>
<td>Upper moderate disability</td>
</tr>
<tr>
<td>Good recovery (May have minor residual neurological and/or psychological deficits)</td>
<td>Lower Good Recovery</td>
</tr>
<tr>
<td></td>
<td>Upper Good Recovery</td>
</tr>
</tbody>
</table>

Table 6. *The summary of Extended Glasgow Outcome Scale (Wilson et al., 1998)*
Although several other scales have been reported similar strength for assessment of neurological outcome of the patients with sTBI: Neurological Outcome Scale (NOS-TBI), Disability Rating Scale (DSR), Functional Independence Measurement (FIM) and Glasgow Outcome at Discharge Scale (GODS) (McCauley et al., 2013, McMillan et al., 2013, van Baalen et al., 2006) the GOS and GOSE remains a golden standard. Both scales are based on a standardised description of patient’s neurological performance allowing the examiner to quickly and easily assess the patient (Wilson et al., 2000, Weir et al., 2012). Even if these scales are rather simple, they allow reproducible and valid assessment of physical outcome of the TBI patients (Hall et al., 2001 and 1985, Jennette at al., 1981).

**Aims**

**General aims:**

- To investigate and characterise the evolution and dynamics of pathological changes on CT and their impact on outcome in patients who sustained sTBI and treated according to ICP targeted therapy protocol.

**Specific aims:**

- To characterise the evolution of intracranial changes using three CT scan classifications (*Paper 1*)
- To investigate whether GCS, ICP and CPP measurements correlate with CT scan classifications (*Paper 1*)
• To investigate whether CT classifications can be used for prognostication (*Paper I)*

• To investigate whether CT scan classifications correlate to the level of biochemical biomarkers of TBI (NSE, S100B) (*Paper II*)

• To explore whether a combination of CT classification together with levels of biochemical biomarkers of TBI can be used for clinical prognostication (*Paper II*)

• To investigate whether the necessity of performing DC can be predicted by combination of Rotterdam score, NSE, S100B, ICP and CPP patterns (*Paper III*)

• To examine the relationship between levels of NSE, S100B, ICP, CPP and Rotterdam score and clinical outcome in patients treated with and without DC (*Paper III*)

• To evaluate the complication frequency after cranioplasty in patients treated with DC as a part of the ICP targeted therapy protocol (*Paper IV*)

• To examine which material used for cranioplasty correlates with higher complication rate (*Paper IV*)

• To examine risk factors predisposing to complication rate after cranioplasty (*Paper IV*)
In preparing for battle I have always found that plans are useless, but planning is indispensable.”

— Dwight D. Eisenhower
**Materials and methods**

**Study I-III**

All patients were previously included in a prospective randomized double-blinded placebo controlled trial on the effect of PGI₂ on the cerebral microcirculation in patients with sTBI (Olivecrona et al., 2012). The patients were included using the following criteria: documented event of sTBI, GCS ≤ 8 at the time of sedation and intubation and age from 15 to 70 years. All patients with initial CPP ≥10 mmHg were included regardless GCS 3 and/or dilated fixed pupils. Patients with an initial CPP < 10 mmHg were regarded as dead on arrival. Patients with penetrating head trauma as well as pregnant or lactating women were excluded. Since there was no statistical significant difference between the groups (control vs. prostacyclin) in regard to age, gender, GCS and GOS at 3, 6, and 12 months the enrolled patients were treated as one group.

**Treatment and monitoring**

All included patients were sedated with midazolam and fentanyl, and were mechanically normoventilated after intubation. All patients received multimodal monitoring including HR, BP, RR, saturation and CVP. Care was taken to maintain normotension and normovolemia by infusion of packed red blood cells, albumin, Ringer's acetate, and glucose solution. CPP and MAP were calculated using a standard monitoring device (Marquette Solar, General Electric Medical System, Milwaukee, Wisconsin, USA). The ICP was
continuously monitored with an intraparenchymal MicroSensor™ (Codman, Johnson & Johnson Professional Inc., Raynham, MA, USA) implanted surgically directly after admission to ICU. The treatment goal was the maintenance of ICP under 20 mmHg. CPP of 50 mmHg was considered a threshold. ICP_{max} was defined as the mean ICP during the one hour with the highest ICP. A similar principle was used to identify CPP_{min}. The mean of the minute-to-minute values for each hour during the first 120 hours were calculated to identify a mean ICP and CPP. Standard blood samples were controlled at least daily. Physiological parameters from the ICU system (Marquette Solar, General Electric Medical Systems) were digitally stored on a computer using the LABpilot software (CMA Microdialysis). Simultaneously, the data were stored in the patient’s case file in the ICU system (Picis, Inc., Wakefield, MA).

*S100B and NSE*

S100B and NSE were collected every 12 hours (twice daily) during the first five days and were stored in a freezer at -70°C. The LIAISON®, a fully automatic system, was used to analyse the blood samples (AB DiaSorin, Sangtec Medical, Bromma, Sweden). The detection range for S100B analysis was 0.02-30 µg/l with an intra- and interassay variation below 5% and 10% respectively; for the NSE analysis, the detection range was 0.04-200 µg/l with an intra- and interassay variation below 3% and 6% respectively. During the first five days, the highest values were identified as S100B_{max} and respective NSE_{max}. The Kaleida Graph software (Synergy Software, Reading,
PA, USA) was used to calculate the area under the curve (AUC) that
calculating the bulk release during the three first days ($S_{100B_{BR}}, NSE_{BR}$).

**CT scan and CT evaluation**

As described earlier, the CT; was performed directly after admission to the
primary receiving hospital. The control CT scan was scheduled
approximately 24 hours after the trauma irrespective of the condition of the
patient. If the clinical condition of the patient required additional CT
investigation, the control CT scan was performed earlier. The $CT_{6d}$ was the
scan obtained closest to sixth day after trauma. The $CT_s, CT_{24}$, and $CT_{6d}$ were
identified in every patient. Thereafter, all the CT scans were classified
according to the Marshall and the Rotterdam classifications. The Morris-
Marshall classification was used to evaluate tSAH in all $CT_s$ and $CT_{24}$.

The post-traumatic changes were described as IPH, ASDH, EDH and tSAH
with or without IVH. The sum of the delineated area of the lesion on each
scan multiplied by slice thickness was used to calculate the volume.

**Outcome**

Independent investigators assessed the outcome using structured interviews.
The outcome was reported as GOS at 3, 6 and 12 months and GOSE at 3 and
6 months.

**Study IV**

Study IV included patients who underwent cranioplasty between 2002 and
2008. All the patients were previously treated according to the ICP targeted therapy including DC after sTBI. The hospital records were reviewed retrospectively. The analysis of the clinical results was performed at least two years after the cranioplasty. The DC was performed according to a previously described routine with a large fronto-temporo-parietal craniectomy measuring approximately 10 to 15 cm long.

The cranioplasty was performed using cryopreserved autologous bone grafts or PMMA. The autologous bone, obtained from the patient during DC, was washed, packed, and frozen at −80 °C. The PMMA was hand-moulded during cranioplasty. The flap was fixed by titanium miniplates regardless the material used during cranioplasty.

**CT evaluation**

The size of the cranioplasty was calculated in order to determine whether the size of the craniectomy has an impact on post-operative complication rate. All pre-operative CT scans were evaluated using the formula for calculating the area of an ellipse \( \pi (A \times B)/4 \) with (A) being the longest anterior-posterior diameter of the craniectomy and (B) being the number of slices covering the craniectomy multiplied by slice thickness.

**Outcome**

The hospital records were reviewed at least 24 months after cranioplasty. All data concerning any postoperative complication were collected, regardless of the necessity for re-operation.
Statistics

In general, continuous variables are reported as means ± SEM and discrete variables as median and range. ANOVA with Bonferroni post-hoc test, and Student’s paired or unpaired two-tailed t test were used for calculations of significant differences between the means. Wilcoxon signed-rank test was used for paired and Wilcoxon rank-sum test for comparison of discrete variables between groups. Chi-squared test was used for proportions. A Log-rank test was used to evaluate differences in survival time. In study IV, Kaplan–Meier diagram was used for estimation of survival of cranioplasty (product-limit method). Spearman’s rho test was used for correlations of categorical variables. The Pearson test was used for comparing proportions. Predictive factors were analysed with logistic regression (uni- and multivariate). In study III a nominal logistic fit analysis was used to explore prognostic factors. In studies I-III, receiver operator characteristics (ROC) analysis was applied for predictability. A p value ≤ 0.05 was considered statistically significant. In studies I-III, all statistical analyses were performed using the JMP™ v.5.0 and 10.0 software (Statistical Analysis System [SAS] Institute; Cary, NC, USA). In study IV, IBM SPSS 21.0 Statistics software was used.
“Success is stumbling from failure to failure with no loss of enthusiasm.”

— Winston S. Churchill
Results

Study I-III

Studies I-III included 48 patients (31 male and 17 female; mean age = 35.5 ± 2.2 years). The median GCS at intubation was 6 (range 3-8). The control and prostacyclin groups had no statistical differences in age (un-paired Student’s t-test), gender (Chi-squared test), GCS, GOS at 3, 6, and 12 months, CT classifications, APACHE II, ISS (Wilcoxon rank-sum test) and S100B and NSE (Spearman rho test). Therefore, the results of all patients were treated as one group. The CTi was performed at 2.6 ± 0.3 hours from the TBI. One patient was excluded because she was discovered 17.8 hours after sustaining the trauma. The mean time between CTi and CT24 investigations was 22.5 ± 1.1 hours. The first sample of biochemical biomarkers was collected at 15.8± 1.1 hours after trauma.

Study I

The mean volume of the EML (ASDH, EDH and IPH) was 45±6.5 ml and 43±6 ml of NEML. 18 of the IPH cases were seen on CTi with a mean volume of 9±4 ml. At CT24, the volume of these lesions had increased to 27±4 ml (p≤0.01, paired Student’s t test). The mean volume of all IPH at CT24 was 30±5 ml. The total volume of IPH at CTi had a statistically significant negative correlation with GOS at 3 (ρ=-0.33, p≤0.02), 6 (ρ=-0.32, p≤0.03), and 12 months (ρ=-0.30, p≤0.05) (Spearman’s rho test). However, the IPH volume at CT24 showed a statistically significant negative correlation only
with GOS at 3 months ($\rho=-0.33$, $p \leq 0.02$, Spearman’s rho test). There was no correlation between IPH and GCS, $ICP_{\text{max}}$ and $CPP_{\text{min}}$. The evaluation of CT before implantation of the microdialysis was done without using any CT classification. According to this assessment, the right hemisphere was considered as the most traumatized in 60% of cases. The assessment according to Marshall classification of the initial images (done blindly to the previous assessment) revealed the right hemisphere as the most traumatized in 56% of the cases. There was a change between CT$_{i}$ and CT$_{24}$ in location of most traumatized hemisphere from right to left in 15% of cases.

The intracranial pathologies are summarized in table 7.

Marshall and Rotterdam classification results demonstrated statistically significant correlation at CT$_{i}$ ($\rho=0.67$, $p \leq 0.0001$) and CT$_{24}$ ($\rho=0.40$, $p \leq 0.005$, Spearman’s rho).

**Marshall CT classification**

The median value of Marshall classification at CT$_{i}$ was 3 and 5 at CT$_{24}$ (range 1-6). There were only two patients without intracranial changes classified as “Diffuse injury I” at CT$_{i}$. However, 18 patients demonstrated intracranial mass lesion with volume extending 25 ml (non-evacuated mass lesions, NEML). In the control CT, only one of the “Diffuse injury I” remained unchanged. Twenty-six patients underwent surgical evacuation of mass lesion (EML), whereas only 17 of these mass lesions were visible at CT$_{i}$. The remaining nine patients were initially classified as “Diffuse injury III” at CT$_{i}$. 

50
Table 7: Types of pathological findings at CT after traumatic brain injury (IPH-intraparenchymal haemorrhage, ASDH-acute subdural hematoma, IVH-intraventricular haemorrhage, EDH-epidural hematoma, tSAH-traumatic subarachnoid haemorrhage)

In order to describe the distribution of post-operative changes, the EML group was re-evaluated. The details of this evaluation are presented in table
Table 8: The result of re-evaluation according to Marshall CT classification of evacuated mass lesion group (EML) at CT<sub>24</sub> (n=26)

<table>
<thead>
<tr>
<th>Number of the patients (n=26)</th>
<th>Marshall classification after re-evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (19%)</td>
<td>Diffuse injury II</td>
</tr>
<tr>
<td>8 (31%)</td>
<td>Diffuse injury III</td>
</tr>
<tr>
<td>3 (11%)</td>
<td>Diffuse injury IV</td>
</tr>
<tr>
<td>10 (38%)</td>
<td>Non-evacuated mass lesion (&gt;25ml)</td>
</tr>
</tbody>
</table>

Rotterdam classification

The median value of Rotterdam classification was 3 both at CT<sub>i</sub> and CT<sub>24</sub> (range 1-5) (p≤0.0001, Wilcoxon signed-rank). According to this classification 23 (48%) of the patients improved, 19 (40%) remained unchanged and 6 (13%) deteriorated at CT<sub>24</sub>.

The distribution of Marshall and Rotterdam classification at CT<sub>i</sub> and CT<sub>24</sub> is presented in figure 5.
Figure 5

![Bar chart showing distribution of Marshall and Rotterdam classifications at CTi and CT24.](image)

Fig. 5 Distribution of Marshall (I, II, III, IV, EML, NEML) and Rotterdam (1, 2, 3, 4, 5) classifications at CT\textsubscript{i} and CT\textsubscript{24}.

**Morris-Marshall classification**

The median value of Morris-Marshall classification was 2 at CT\textsubscript{i} and CT\textsubscript{24} (range 0-4). The distribution of Morris-Marshall classification at CT\textsubscript{i} and CT\textsubscript{24} is presented in figure 6.

The CT\textsubscript{i} revealed tSAH in 32 (67\%) of the patients. This increased to 34 (73\%) on the 24-hour investigation. IVH was observed in 16 (33\%) of the patients at CT\textsubscript{i} and 25 (52\%) at CT\textsubscript{24}. 
ICP\textsubscript{max}, CPP\textsubscript{min} and GCS

The only statistical significant correlation was demonstrated between ICP\textsubscript{max} and Morris-Marshall at CT\textsubscript{24} ($\rho=-0.32$, $p \leq 0.03$) (Spearman’s rho test).

Outcome

All CT classifications demonstrated statistically negative correlation at CT\textsubscript{i} with GOS at 3, 6 and 12 months (Spearman’s rho test). The Rotterdam classification showed strongest correlation at 3 months. The details of the correlation are summarized in table 9.
Table 9

<table>
<thead>
<tr>
<th>GOS</th>
<th>Marshall classification</th>
<th>Rotterdam classification</th>
<th>Morris-Marshall classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>$\rho = -0.32, p \leq 0.03$</td>
<td>$\rho = -0.48, p \leq 0.0006$</td>
<td>$\rho = -0.44, p \leq 0.002$</td>
</tr>
<tr>
<td>6</td>
<td>$\rho = -0.32, p \leq 0.03$</td>
<td>$\rho = -0.39, p \leq 0.004$</td>
<td>$\rho = -0.37, p \leq 0.009$</td>
</tr>
<tr>
<td>12</td>
<td>$\rho = -0.34, p \leq 0.02$</td>
<td>$\rho = -0.41, p \leq 0.004$</td>
<td>$\rho = -0.37, p \leq 0.01$</td>
</tr>
</tbody>
</table>

Table 9: Summarised distribution of negative correlation between CT classification at CT$_i$ and outcome reported as GOS at 3, 6 and 12 months (Spearman’s rho test)

At CT$_{24}$, only Rotterdam and Morris-Marshall classifications showed negative correlation to outcome. Similar to the CT$_1$ results, Rotterdam classification at 3 months presented the strongest correlation. Table 10: summarizes the details of the correlation.
Table 10: *Summarised distribution of negative correlation between CT classification at CT\(_{24}\) and outcome reported as GOS at 3, 6 and 12 months (Spearman's rho test)*

<table>
<thead>
<tr>
<th>GOS</th>
<th>Marshall classification</th>
<th>Rotterdam classification</th>
<th>Morris-Marshall classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>NONE</td>
<td>$\rho = -0.47, p \leq 0.0007$</td>
<td>$\rho = -0.47, p \leq 0.007$</td>
</tr>
<tr>
<td>6</td>
<td>NONE</td>
<td>$\rho = -0.37, p \leq 0.01$</td>
<td>$\rho = -0.38, p \leq 0.007$</td>
</tr>
<tr>
<td>12</td>
<td>NONE</td>
<td>$\rho = -0.38, p \leq 0.007$</td>
<td>$\rho = -0.31, p \leq 0.03$</td>
</tr>
</tbody>
</table>

Dichotomization of GOS (dead or alive) showed no statistical difference at CT\(_i\). However, Rotterdam at 6 months showed statistically significant difference ($p<0.05$) and Morris-Marshall demonstrated significant difference after dichotomization at 3 ($p=0.05$), 6 ($p \leq 0.02$) and 12 months ($p \leq 0.02$) (Wilcoxon rank-sum test). The contingency analysis revealed statistically significant difference in the distribution of Rotterdam classification but not Morris-Marshall and GOS at 3 months ($p \leq 0.003$ Pearson's test). Parallel analysis showed no statistical significance with Marshall classification.

*Prognostication*

To investigate the prognostic factors for clinical purposes the CT classifications (Marshall, Rotterdam and Morris-Marshall) were used as independent factors and GOS as dependent factors. Regression analysis
demonstrated that CT\textsubscript{i} findings statistically significantly predicted outcome as GOS at 3 (p ≤ 0.01), 6 (p ≤ 0.05), and 12 (p ≤ 0.05) months. The Rotterdam classification was the best predicting factor at 3 and 6 months and the Morris-Marshall was the best predicting factor at 12 months. When dichotomization (dead and alive) was used, the regression analysis showed no significant prediction of outcome. ROC analysis after dichotomization (dead and alive) showed an AUC of 0.722 with Rotterdam classification and CT\textsubscript{i}. Rotterdam 4 showed the highest accuracy with sensitivity of 0.857 and specificity of 0.634. Marshall Diffuse injury III showed a sensitivity of 1.000 and a specificity of 0.268. Morris-Marshall class 3 showed highest sensitivity and specificity (respective 0.833 and 0.571 respectively). AUC for Morris-Marshall classification was 0.744. Similar analysis of CT\textsubscript{24} results showed lower AUC in all classifications.

**Study II**

The Marshall CT classification demonstrated statistically significant correlation with with S\textsubscript{100B\textsubscript{72h}} and NSE\textsubscript{BR} at CT\textsubscript{i} and NSE\textsubscript{72h} both at CT\textsubscript{i} and CT\textsubscript{24}. Rotterdam classification showed correlation at CT\textsubscript{i} with S\textsubscript{100B\textsubscript{BR}} and at CT\textsubscript{24} with S\textsubscript{100B\textsubscript{72h}}, S\textsubscript{100B\textsubscript{BR}} and NSE\textsubscript{BR}. The Morris-Marshall classification correlated to all S\textsubscript{100B} variables, but not to a single NSE variable for both CT\textsubscript{i} and CT\textsubscript{24} (Spearman’s rho correlation). The summary of correlations between CT classifications and S\textsubscript{100B} and NSE are presented in table 11 and 12.
<table>
<thead>
<tr>
<th>$S_{100B}$</th>
<th>Marshall $CT_i$</th>
<th>Marshall $CT_{24}$</th>
<th>Rotterdam $CT_i$</th>
<th>Rotterdam $CT_{24}$</th>
<th>Morris-Marshall $CT_i$</th>
<th>Morris-Marshall $CT_{24}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_{100B_{init}}$</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>$\rho=0.3069$, $p=0.0339$</td>
<td>$\rho=0.3183$, $p=0.0275$</td>
</tr>
<tr>
<td>$S_{100B_{init}}$</td>
<td>$\rho=0.4567$, $p=0.0014$</td>
<td>$\rho=0.3159$, $p=0.0324$</td>
<td>NS</td>
<td>$\rho=0.3963$, $p=0.0064$</td>
<td>$\rho=0.3686$, $p=0.0117$</td>
<td>$\rho=0.3384$, $p=0.0214$</td>
</tr>
<tr>
<td>$S_{100B_{init}}$</td>
<td>NS</td>
<td>NS</td>
<td>$\rho=0.2904$, $p=0.0453$</td>
<td>$\rho=0.3878$, $p=0.0065$</td>
<td>$\rho=0.4816$, $p=0.0005$</td>
<td>$\rho=0.4188$, $p=0.0030$</td>
</tr>
<tr>
<td>$S_{100B_{max}}$</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>$\rho=0.3443$, $p=0.0166$</td>
<td>$\rho=0.3054$, $p=0.0348$</td>
</tr>
</tbody>
</table>

Table 11: Summary of correlation between CT classifications (Marshall, Rotterdam and Morris-Marshall) at $CT_i$ and $CT_{24}$ and $S_{100B}$. The level of $S_{100B}$: at initial, 72 hours, bulk release (BR) and maximal (max). $\rho$: Spearman’s rho correlation coefficient; NS: non-significant.
### Table 12

<table>
<thead>
<tr>
<th></th>
<th>Morris-Marshall</th>
<th>Rotterdam</th>
<th>Marshall</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT 24</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CT 1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>ρ=0.2894, p=0.0485</td>
</tr>
<tr>
<td>NSE init</td>
<td>NS</td>
<td>NS</td>
<td>ρ=0.3664, p=0.0104</td>
</tr>
<tr>
<td>NSE 72h</td>
<td>NS</td>
<td>NS</td>
<td>ρ=0.3488, p=0.0151</td>
</tr>
<tr>
<td>NSE max</td>
<td>NS</td>
<td>NS</td>
<td>p=0.0411</td>
</tr>
</tbody>
</table>

Table 12: Summary of correlation between CT classifications (Marshall, Rotterdam and Morris-Marshall) at CT 24 and CT 1, and NSE. The level of NSE: at initial, 72 hours, bulk release (BR) and maximal (max). ρ: Spearman's rho correlation coefficient, NS: non-significant
S100B and NSE demonstrated statistically significant correlation to ICP_{max} and CPP_{min}. The strongest correlation was with bulk release and maximal values of both S100B and NSE. Details about ICP_{max} and CPP_{min} correlation to S100B and NSE are summarized in table 13 and 14.

**Table 13**

<table>
<thead>
<tr>
<th></th>
<th>S100B_{init}</th>
<th>S100B_{72h}</th>
<th>S100B_{max}</th>
<th>S100B_{BR}</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP_{max}</td>
<td>r=0.52, p&lt;0.0005</td>
<td>r=0.39, p&lt;0.01</td>
<td>r=0.69, p&lt;0.001</td>
<td>r=0.69, p&lt;0.0001</td>
</tr>
<tr>
<td>CPP_{min}</td>
<td>r=-0.46, p&lt;0.005</td>
<td>r=-0.26, n.s.</td>
<td>r=-0.63, p&lt;0.0001</td>
<td>r=-0.58, p&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 13: *Summary of correlation between S100B and ICP\textsubscript{max} and CPP\textsubscript{min}.*

Logarithmic values for the biomarker were used in calculation of r and p. (Pearson’s correlation). p<0.05 was regarded as statistically significant.

**Table 14**

<table>
<thead>
<tr>
<th></th>
<th>NSE_{init}</th>
<th>NSE_{72h}</th>
<th>NSE_{max}</th>
<th>NSE_{BR}</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP_{max}</td>
<td>r=0.37, p&lt;0.05</td>
<td>r=0.27, p&lt;0.0623</td>
<td>r=0.57, p&lt;0.0001</td>
<td>r=0.50, p&lt;0.0005</td>
</tr>
<tr>
<td>CPP_{min}</td>
<td>r=-0.34, p&lt;0.05</td>
<td>r=-0.21, n.s.</td>
<td>r=-0.56, p&lt;0.0001</td>
<td>r=-0.48, p&lt;0.001</td>
</tr>
</tbody>
</table>

Table 14: *Summary of correlation between NSE and ICP\textsubscript{max} and CPP\textsubscript{min}.*
p<0.05 was regarded as statistically significant. Logarithmic values for the
biomarker were used in calculation of r and p. (Pearson’s correlation); n.s. non significant

ROC analysis was used to evaluate prediction values of the biochemical biomarker release. The highest AUC in the ROC analysis was due to bulk release of biomarkers and the concentration at 72h after injury. There was no statistically significant difference between S100B and NSE in the ROC curves. Morris-Marshall at CTi and S100B86 were added to further improve the prognostication resulting in increased power of prediction (AUC=0.8929, p=0.0008). The cut-off value (μg/l) is the biochemical biomarker level, where the combination of the highest sensitivity and specificity is found. The outcome was dichotomized into dead or alive at 3 months after sTBI. The details of ROC analysis regarding biochemical biomarkers are described in table 15 (S100B) and in table 16 (NSE).
Table 15: Summary of ROC analysis regarding S100B

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>S100B_{init}</th>
<th>S100B_{72h}</th>
<th>S100B_{BR}</th>
<th>S100B_{max}</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>0.6865</td>
<td>0.7976</td>
<td>0.8333</td>
<td>0.7917</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>1.0000</td>
<td>0.7500</td>
<td>0.8333</td>
<td>0.8333</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.3810</td>
<td>0.9048</td>
<td>0.8250</td>
<td>0.7870</td>
</tr>
<tr>
<td>Cut-off (µg/L⁻¹)</td>
<td>0.540</td>
<td>0.650</td>
<td>3.815</td>
<td>1.150</td>
</tr>
<tr>
<td>p Value</td>
<td>0.0074</td>
<td>0.0078</td>
<td>0.0009</td>
<td>0.0029</td>
</tr>
</tbody>
</table>

Table 16: Summary of ROC analysis regarding NSE

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>NSE_{init}</th>
<th>NSE_{72h}</th>
<th>NSE_{BR}</th>
<th>NSE_{max}</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>0.7276</td>
<td>0.8476</td>
<td>0.8167</td>
<td>0.8135</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.5000</td>
<td>1.0000</td>
<td>1.0000</td>
<td>1.0000</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.9268</td>
<td>0.9048</td>
<td>0.5250</td>
<td>0.5238</td>
</tr>
<tr>
<td>Cut-off (µg/L⁻¹)</td>
<td>37.220</td>
<td>6.2500</td>
<td>40.440</td>
<td>40.440</td>
</tr>
<tr>
<td>p Value</td>
<td>0.0192</td>
<td>0.0045</td>
<td>0.0190</td>
<td>0.0181</td>
</tr>
</tbody>
</table>

Study III

Nineteen of the above mentioned 48 patients required DC (16 unilateral and 3 bilateral). However, three patients were excluded for the following reasons:
one underwent DC very late (160 hours) after sTBI, which is highly unusual, and two were acutely operated on at a local hospital (i.e., severe brain swelling required that the bone flap be left unattached before transfer to our unit) for life threatening ASDH. Because of a severe brain swelling the bone flap was left out before the transfer to our unit. Exclusion of these patients did not affect the general results. The median time of DC was 12 hours (range 1-160). In seven patients initial craniotomy for evacuation of intracranial pathology was converted to DC due to massive cerebral oedema. The median time to DC in the converted group was 9 and 26 hours in the regular DC group (p=0.008, Wilcoxon rank-sum test). The mean size of the unilateral DC was $82 \pm 4 \text{ cm}^2$ and $130 \pm 28 \text{ cm}^2$ in bilateral ones.

The mean time between the trauma and CT$_1$ was $2.6 \pm 0.3$ hours. The corresponding time between CT$_1$ and CT$_{24}$ investigations was $22.5 \pm 1.1$ hours. We analysed the sub-groups to rule out the eventual discrepancies between results of converted and regular DC. There was no significant influence on the results, so we analysed the DCs as one group. The median GCS in NDC group was 6 (3-8) and the median GCS in the DC group was 5 (3-8).

ICP and CPP

During first day in the DC group, ICP$_{\text{max}}$ was higher (p<0.002) and CPP$_{\text{min}}$ lower (p<0.02) than in the NDC group (two-tailed unpaired Student’s t-test). ICP in the DC group manifested much higher values. DC resulted in a rapid decrease in ICP.
Details of the ICP and CPP values in both groups are summarized in table 17.

Table 17

<table>
<thead>
<tr>
<th>Values in mmHg</th>
<th>DC (n=16)</th>
<th>NDC (n=29)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ICP&lt;sub&gt;days 1-5&lt;/sub&gt;</td>
<td>20.4±3.8</td>
<td>15.4±0.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>ICP&lt;sub&gt;max days&lt;/sub&gt;</td>
<td>32.3±4.2</td>
<td>20.5±1.1</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>ICP&lt;sub&gt;max days 2&lt;/sub&gt;</td>
<td>28.4±5.3</td>
<td>21.4±1.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>ICP&lt;sub&gt;max days 1-5&lt;/sub&gt;</td>
<td>35.4±4.9</td>
<td>24.5±0.93</td>
<td>&lt;0.007</td>
</tr>
<tr>
<td>Mean CPP&lt;sub&gt;days 1-5&lt;/sub&gt;</td>
<td>63.4±3.7</td>
<td>66.1±1.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>CPP&lt;sub&gt;min days&lt;/sub&gt;</td>
<td>45.7±2.8</td>
<td>51.8±1.0</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>CPP&lt;sub&gt;min days 2&lt;/sub&gt;</td>
<td>49.5±4.1</td>
<td>51.6±1.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>CPP&lt;sub&gt;min days 1-5&lt;/sub&gt;</td>
<td>42.9±3.9</td>
<td>47.5±1.3</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Table 17. Summary of ICP and CPP values in the decompressive craniectomy (DC) and non-decompressive craniectomy (NDC) groups. Values are presented as means ± SEM

CT classification

In the DC group, the Rotterdam score was statistically significantly higher at CT<sub>i</sub> (p<0.0002), CT<sub>24</sub> (p<0.06, ns), and CT<sub>60</sub> (p<0.002) (Wilcoxon rank-sum test).

Biochemical Biomarkers

S<sub>100B</sub> levels showed a statistically significant difference between the non-
decompressive craniectomy (NDC) and DC groups at all the investigated
time-points including the $S_{100B_{BR}}$ and $S_{100B_{max}}$ (un-paired two-tailed
Student’s t-test).

Only NSE$_i$ (p<0.02) and NSE$_{max}$ (p<0.005) levels showed a statistically
significant difference between the DC and NDC groups (un-paired two-tailed
Student’s t-test).

DC prediction

A nominal logistic fit model showed that the combination of ICP$_{max \ day1}$,
Rotterdam CT$^i$ score and the first NSE and S$_{100B}$ are prognostic factors for
the need of a DC (p<0.0001). The Rotterdam score contributed most to the
model and this was followed by ICP$_{max}$ and S$_{100B}$. The following analysis
with receiver operating characteristic analysis (ROC) demonstrated an AUC
of 0.931, a sensitivity of 1.000 and a specificity of 0.750.

Outcome

The outcome in the DC group was worse. There was no statistically
significant difference in outcome between the converted and regular DC
groups. The median GOSE at 6 months was 5 (range 3-8) in the NDC group
and 3 (range 1-8) in the DC group (p<0.005, Wilcoxon rank-sum test). At six
months, the DC group presented with mortality of 43.7 % as compared to 0
% in the control group at 6 months (p<0.001, Wilcoxon rank-sum test).
Study IV

The study included 49 patients (38 male and 11 female; mean age 43.2±16.1; range 3–77 years) who were treated with cranioplasty between 2002-2008. The mean time between DC and cranioplasty was 3.8±2.6 months (range 1–13). The mean follow-up time was 54.3±25.9 months (range 24–100). The patients were divided into two groups depending on type of the implanted material: 30 (61.2%) patients received autologous bone and 19 (38.8%) patients received PMMA. There was no statistically significant difference in mean age between the groups (40.2 ±16.3 years for autologous bone and 45.4±15.8 years for PMMA, p=0.28, two-tailed, unpaired t-test) or in the male/female ratio (24 (80%) for autologous bone and 14 (74%) for PMMA, p=0.73, Chi-square test). Five patients in autologous bone group and six in PMMA group received ventriculo-peritoneal shunt before cranioplasty (p=0.22, two-tailed, unpaired t-test). The mean size of the implanted flap (cm²) was 66.7±24.7 for the autologous bone group and 68.8±19.4 for the PMMA group (p=0.80, ANOVA). There was a statistically significant difference in time between DC and cranioplasty between the groups: 3.2±1.6 months (autologous bone) vs. 4.8±3.6 months (PMMA) (p=0.04, ANOVA).

The overall complication rate was 40.8% (20 patients). A mean time to re-operation after cranioplasty was 11.7±18.5 months (range 0.03–80).

Details of complications in both groups are shown in table 18.
Table 18: Summary of complication rate in autologous bone and PMMA groups. Statistical significance: \((p<0.05)\)

<table>
<thead>
<tr>
<th></th>
<th>Post-op haematoma (%)</th>
<th>Infection (%)</th>
<th>Dislodgement (%)</th>
<th>Resorption (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous bone group</td>
<td>6 (12.2%)</td>
<td>3 (6.1%)</td>
<td>1 (2.03%)</td>
<td>6 (12.2%)</td>
</tr>
<tr>
<td>PMMA group</td>
<td>0</td>
<td>2 (4.1%)</td>
<td>2 (4.1%)</td>
<td>0</td>
</tr>
<tr>
<td>P value</td>
<td>0.04</td>
<td>0.65</td>
<td>0.33</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Outcome

The autologous bone group had a significantly higher rate of complications (16/30, 53.3%) compared to the PMMA group (4/19, 21.1%) \((p=0.03\), Chi-square test\). Six of the patients who were treated with autologous bone cranioplasty (6/30, 20%) developed bone resorption according to a CT scan. The mean time of resorption was 25.33±21.21 months (range 7–80). There was no significant statistical difference in age between patients with bone resorption (30.5±10.3 years) and those without resorption (42.6±16.8 years, \(p = 0.10\), range 14–41, two-tailed, unpaired t-test). Furthermore, the autologous bone group presented with a significantly higher rate of postoperative haematomas that occurred early after cranioplasty (mean time 0.48±0.76 months) \((p<0.05\), ANOVA\).
The PMMA cranioplasty had a longer mean survival time (79.5±9.0 months) compared to autologous bone (48.1±7.8 months), (p = 0.035, Log-rank test). The cranioplasty material was also the only statistically significant variable associated with a complication requiring re-operation (autologous bone vs. PMMA, p = 0.03, Logistic regression, univariate analysis). The difference in time from DC to cranioplasty between the bone and PMMA group was close to significant (p = 0.06, Logistic regression, univariate analysis). However, in a multivariate model none of these parameters showed a significant difference although the choice of material was close to significant (p = 0.08, Logistic regression, multivariate analysis).
“It infuriates me to be wrong when I know I'm right.”

— Molière
Discussion

The changes in the management of sTBI started with understanding that traumatic injury of the brain tissue initiates a cascade of self-perpetuating events responsible for further damage. Measures taken to minimize the negative effects of this vicious cascade resulted in decreased mortality from 35-50% (Langfitt et al. 1982, Nordström et al., 1989) to 10-15% with 60-70% good outcome (Olivecrona at al. 2009, Naredi et al. 2001). Thus, the outcome after sTBI in a modern neurointensive care setting largely depends on early diagnostics, medical stabilization of the patients and surgical evacuation of space occupying mass lesions. Careful monitoring and repeating of diagnostics are essential for identifying, preventing and aggressively treating any secondary insults and/or complications that can impede recovery. The goal of modern intensive care management is to provide the brain an optimal environment for recovery. This goal emphasizes the need for a CT classification that can be used for repeated re-evaluation and prognostication.

CT classifications

Our results demonstrate that Marshall is applicable for evaluation of initial images and it correlates to outcome. These findings correspond with the results reported by Hiler et al. (Hiler et al., 2006). However, the disadvantage of Marshall classification in clinical setting is that correlation as well as prognostication strength disappears with 24 hours CT. Moreover, Marshall classification ignores a very distinct pathological entity: tSAH. The tSAH plays important role in the pathophysiological chain reaction after
sTBI. The tSAH and IVH are changes that were observed in vast majority of the patients in our material (67%). Even a larger number of patients demonstrated these haemorrhages at control images (73%). Chieregato et al. presented similar findings in their material (Chieregato et al., 2005). It remains unclear whether these haemorrhages are due to redistribution of the blood or due to new bleedings. Many studies highlight the tSAH as a negative prognostic factor due to an advert effect on the cerebral blood flow (vasospasm) and inflammatory changes after sTBI (Greene et al., 1997, Lee et al., 1997, Mattoli et al., 2003, Soustiel et al., 2004, Oertel et al., 2005). Because of these studies we decided to use the Morris-Marshall classification designed to quantify the severity of tSAH. Surprisingly, despite being limited to only tSAH, Morris-Marshall classification shows stronger negative correlation to outcome on CT\textsubscript{1} than the Marshall classification. Furthermore, Morris-Marshall classification also shows strong statistically significant negative correlation to outcome on CT\textsubscript{24}. It can be easily used for re-evaluation of the CT images. Our results are in-line with other study (Mattioli et al., 2003).

The Rotterdam score was introduced in order to address the disadvantages of the Marshall classification (Maas et al., 2005). As a mathematical score, the Rotterdam classification can easily be used for multiple re-evaluations. Furthermore, it recognizes the tSAH as one of the pathological entities that indicate the severity of TBI. We were able to demonstrate that Rotterdam score has a negative correlation with outcome both at initial and control images.
Treatment of sTBI according to our protocol requires sedation. Since clinical examination and neurologic status are difficult to conduct in correct manner because of intubation and sedation the recognition and interpretation of early signs of deterioration are crucial for successful therapy. Our analysis of initial and control CT images clearly demonstrates that only a small fraction of them remain unchanged. The brain parenchyma may look normal at initial images, but it can “transform” during the first 24 hours and appear injured at the control images. The cerebral contusions and IPH are primary traumatic lesions with tendency to increase in volume and these can become space occupying mass lesions. We have observed this evolution in almost 40% of all patients, which is a much larger number than previous reported (Lobato et al., 1997, Servadei et al., 2000). However, our study enrolled only the most severe traumatised patients with GCS ≤ 8 and included individuals with uni- and bilateral dilated pupils as long as their CPP was ≥ 10 mmHg. The evolution and transformation of mass lesion might continue even after the surgery. The EML (IPH, EDH and ASDH) as described in Marshall classification does not guarantee the stabilization of the pathological changes. The re-evaluation of the images of the EML group confirms our hypothesis that almost 50% of them can still be classified as surgical candidates. Taken together we propose that CT scans are systematically evaluated using standard classification system and repeated at least 24 hours after the injury. This enables proper comparison of CT images and may be used in prognostication of outcome. Another misconception is that ICP will always be low after surgical evacuation of a large intracranial haematoma. Intracranial hypertension occurs in 50% to 70% of patients after evacuation
of an intracranial haematoma (Miller et al., 1977). This postoperative intracranial hypertension may be due to a new postoperative haematoma (either at the site of the operation or at a new site), diffuse cerebral oedema or focal intraparenchymal lesion. Difficulties in interpretation of signs and symptoms of deterioration have an important impact on clinical decision. The ultimate clinical tool would detect the deterioration on biochemical level before changes appear on CT scan and/or elevation of ICP.

CT classifications and biochemical biomarkers

It is speculated that S100B secondary release could be used to monitor intracranial pathological evolution and thus improve prognostication (Pezold et al., 2002, Pelinka et al., 2003, Raabe et al., 2003, Thelin et al., 2013). Our results confirm correlation between evolution of pathological changes visible on initial and control CT images and S100B. Marshall classification demonstrates statistical significant correlation to S100B at 72 hours both on CT\textsubscript{i} and CT\textsubscript{24}, although findings on Rotterdam CT\textsubscript{i} correlated only to S100B bulk release. On the other hand, Rotterdam classification on CT\textsubscript{24} correlates to S100B both at 72 hours and bulk release. S100B release is known to be associated with the extend of SAH (Vos et al., 2006, Jung et al., 2013). Due to the fact that tSAH occurs on both CT\textsubscript{i} and CT\textsubscript{24} in almost 70% of our patients, the Morris-Marshall classification correlates to all S100B at all sampling time-points but not to even single NSE sample. When it comes to NSE the correlation between Marshall and Rotterdam demonstrates a different pattern with statistical significant correlation at 72 hours and a bulk
release. This heterogeneity in correlation between S100B and NSE probably reflect divergent aspects of pathological changes. The early peak of NSE may reflect the response to immediate damage due to the impact with mechanical disruption of neuronal tissue (Zink et al., 1996). These findings are corroborated with the results of an experimental study (Hårdemark et al., 1989). Pleines et al. concluded, that S100B should be regarded as a “true” damage marker and the NSE mirrors inflammatory reaction initiated by trauma (Pleines et al., 2001). Despite being rather specific for neuronal damage NSE levels can be compromised by haemolysis (Schmitt et al., 1998, Boomfield et al., 2007). On the other hand S100B has two sources: intracranial and extracranial. The first sample of S100B should not be collected too soon after trauma (6-12 hours) as this will make it difficult to distinguish CNS and peripheral S100B sources. Raabe et al. suggested that a high concentration of S100B that exceeds half-life indicates injured BBB (Raabe et al., 1999). However, Bellander et al. reported no correlation between S100B release and activation of C5b9 complex suggesting that S100B is actively released due to on-going cellular damage (Bellander et al., 2011).

The correlation between volume and progression of IPH and biochemical biomarkers has been reported (Herrmann et al., 2000, Pleines et al., 2001, Raabe et al., 2003). This is important in clinical setting since rapid evolution of IPH can lead to medically refractory intracranial hypertension and inevitable surgical evacuation of mass lesion. We found a significant negative correlation between IPH volume at CTi and CT24 and outcome presented as
The pathophysiological mechanisms of major secondary brain damage start to occur on a cellular level. It begins with a phase of cytotoxic injury followed by a vasogenic phase that eventually leads to increased intracranial pressure. The elevated ICP then leads to decreases in the CPP and subsequent further ischemic injury. A reliable marker that allows quantifying the extent of cytotoxic injury could potentially enable initiation therapy before development of the pathological cascade leading to intracranial hypertension and changes seen on the CT scan and/or during neurological examination. It has been suggested that multiple measurements of S100B could forecast secondary injuries (Stein et al., 2011, Thelin et al., 2013). Our findings indicate a strong correlation between CT findings and biochemical biomarkers. Nevertheless, currently there is no consensus, whether release of biochemical biomarkers precede CT changes or vice versa (Romner et al., 2000, Raabe et al. 2003, Unden et al. 2007, Stein et al., 2011). However, we agree with Undén et al. that kinetics of biochemical biomarkers released in relation to pathological changes is a complex process in which it is the cumulative values of biochemical biomarkers that mirror the severity of the on-going process and not the concentration of the single sampling (Undén et al., 2007).

**CT classifications and ICP**

The continuous ICP monitoring is still crucial due to the fact that up to 77% of patients with ICP below 15 mmHg might have a favourable outcome as
compared with just 43% of patients with ICP above 15 mmHg (Marshall et al., 1979). The mortality rate in patients with refractory ICP (irreducible below 20 mmHg) increases from 18% to 92% and the frequency of good outcomes decreases from 74% to 3% in comparison to patients with normal ICP (Miller et al., 1981). Interestingly, Morris-Marshall is the only CT classification that shows a correlation to ICP$\text{max}$ on CT$\text{24}$ despite visible progression of intracranial pathologies. In our opinion, this finding reflects the impact of cytotoxic response of the brain parenchyma to tSAH on intracranial dynamics (Pleines et al., 2001). We were unable to demonstrate correlation between GCS, ICP and CPP and the volume of IPH, which can be explained by initiation of ICP targeted therapy and surgical treatment of pathological, intracranial masses.

**Biochemical biomarkers and ICP**

In accordance with previous reports, we found, that both maximal values of ICP and minimal values of CPP correlate with S100B and NSE (Pelinka et al., 2003, Murillo-Cabezas et al., 2010, Thelin et al., 2013, Olivecrona et al., 2014). ICP$_{\text{max}}$ and CPP$_{\text{min}}$ correlate significantly to both bulk release and maximal concentration values of S100B and NSE. There is no correlation between biochemical biomarkers concentration at 72 hours and ICP$_{\text{max}}$ and CPP$_{\text{min}}$ values. This is intriguing in a light of a strong correlation between biomarkers and all three CT classification at 72 hours. This finding might suggest that the CT evolution precedes neurological deterioration as suggested by other authors (Herrmann et al., 2000, Petzold et al., 2002, Stein et al., 2011). Monitoring of ICP patterns together with CT classification
supports the clinical evaluation, but these usually demonstrate an already “on-going” pathological evolution. The biggest advance in incorporating the S100B and NSE sampling in NICU therapy would be if secondary release peak level of S100B and NSE could predict an ICP elevation and risk for hypoperfusion as suggested by some authors (Thelin et al., 2014, Stein et al., 2012). We suggest that S100B and NSE sampling should be a routinely checked side to side with continuous ICP monitoring and repeated CT imaging in patients with sTBI requiring treatment at NICU.

CT classifications, biochemical biomarkers and outcome prognostication

One of the goals of this dissertation was to investigate whether the CT scan classifications together with biochemical biomarkers can be of importance in the prognostication of outcome. The initial CT findings statistically significantly predicted outcome evaluated as GOS at 3, 6, and 12 months. The Rotterdam classification presented strongest prediction power at 3 and 6 months and the Morris–Marshall at 12 months. Moreover ROC analysis after dichotomization to dead or alive showed that CT, Rotterdam score had strongest prediction value as well as highest sensitivity and specificity. These results support previous studies (Maas et al., 2005 and 2007, Marmarou et al., 2007, Talari et al. 2016) that found the Rotterdam score useful not only to evaluate the severity of the intracranial injury but also, and more importantly to predict the outcome. We were able to confirm that biochemical biomarkers make it possible to predict the outcome after sTBI. The outcome measured as GOSE at 3 months demonstrates negative
correlation to concentrations of S100B and NSE. The strongest correlation was evident in bulk release and 72 hours value of the biochemical biomarkers, findings that confirm the previously reported results (Raabe et al., 1999, Woertgen et al., 1999, Murillo-Cabezas et al., 2010, Pleines et al., 2001). Using ROC analysis, we have showed the highest AUC for the bulk release and 72h values of NSE and S100B. This is in-line with other publications revealing strong correlation between levels of biomarkers temporarily collected and reported close to 72 hours after trauma as well as cumulative measurements of biochemical biomarkers (Herrmann et al., 2000, Murillo-Cabezas et al., 2010).

Taken together, there is no accepted valid method available to quantify the degree of tissue damage following sTBI. The clinical decision is far more complex and depends on a combination of the following factors: clinical examination, radiological imaging, multimodal monitoring and an increased level of various tissue markers such as S100B, NSE as well as microdialysis measurements. By integrating these parameters one might improve the long-term prognosis for TBI patients.

**CT classifications, biochemical biomarkers and DC**

According to our protocol elevated ICP ensues control CT scan and re-evaluation of therapy steps. The evolution of the intracranial haemorrhages together with elevated ICP (despite maximal medical treatment) usually contributes to decision about DC. It is crucial to perform this procedure in order to reverse the negative spiral of secondary insults before irreversible
changes occur, albeit it has an enormous impact on the brain’s physiology. It is imperative to understand that decision about DC must be followed with specific postoperative management and this plays an important role in dictating the success of the procedure. Sudden improvement in brain compliance in circumstances of impaired autoregulation can lead to secondary hyperaemia (Cooper et al., 1979, Timofeev et al., 2008). This may explain the failure in decreasing of cerebral oedema up to 20% of DCs, associated with unfavourable results (Aarabi et al., 2006, Williams et al., 2009). Therefore, modern management strategy should prevent excessive hypertension to counteract the reactive hyperaemia. Moreover, DC is not free from postoperative complications such as infection, postoperative haematomas and new intraparenchymal lesions (Aarabi et al., 2006, Honeybul et al., 2010, 2011). Additionally, DC requires a secondary surgical treatment with cranioplasty, a procedure associated with significant postoperative complications. In our study, 30% of our patients required DC. The ICP at the time of the surgery was generally higher in the DC group compared to the NDC group. The Rotterdam score was higher in the DC group on CT, and CT6d than in the NDC group indicating that patients in DC group sustained more extensive injury. The continuous monitoring of ICP after DC has been shown to influence survival rate and in-hospital mortality. Thus, the protocol guided therapy should be applied even after the DC is performed (Huang et al. 2015).

ICP, CPP and DC

Our analysis of the ICP pattern revealed a statistical significant association
between day 1 $I_{CP_{\text{max}}}$, $I_{CP_{\text{max}}}$ days 1-5, and DC. Second day $I_{CP_{\text{max}}}$ demonstrates no association. To explain this phenomenon, one may speculate that the second day $I_{CP_{\text{max}}}$ is a result of therapeutic interventions, a hypothesis supported by the fact that the median time of the performed DCs was around 12 hours after sustained sTBI. Olivecrona et al. described a pattern of ICP that decreases after DC in order to gradually increase during the following approximately 24 hours, and stabilize at a new lower level (Olivecrona et al., 2007). Furthermore, the clinical signs of secondary insults leading to the refractory intracranial hypertension may not yet been detected. The pathophysiological mechanisms begin to occur on a cellular level before alterations in ICP, neurological examination or neuroimaging. The ICP can appear to be normalized simply because of a “window” between the positive effects of surgical intervention and on-going adverse effects of secondary insults. On the contrary, CPP ($CPP_{\text{min}}$ and $CPP_{\text{mean 5 days}}$) and $MAP_{\text{mean}}$ demonstrate no association to the DC group. This lack of association is most probably due to the fact that the treatment algorithm stipulates that CPP is not allowed to be below 50 mmHg. On the other hand, CPP might be reduced by the ICP elevation above 20 mmHg. Reduced cerebral compliance and elevated ICP causes further disturbance in cerebral microvascular circulation. Normally, smooth muscle tone in the walls of cerebral arteries and arterioles can react to changes in transmural pressure. Patients with injured autoregulation may not tolerate higher CPP because increased arterial blood pressure will lead to increased CBV and CBF and further elevation of ICP (Czosnyka et al., 1996). In case of DC, which may improve the compliance but can lead to hyperaemic reperfusion, the impaired
microvascular autoregulation may aggravate the oedema (Panerai et al., 2008, Rangel-Castilla et al., 2008, Zweifel et al., 2008). This aggravation might explain why the CPP targeted therapy does not seem to improve outcome after sTBI but is associated with much higher frequency of acute respiratory distress syndrome (Robertson et al., 1999 and 2001). On the contrary, Johnson et al. demonstrated that patients treated with lower CPP threshold levels had better outcome (Johnson et al., 2011). One can speculate that by normalization of the MAP in order to reduce the capillary hydrostatic pressure a decreased the influx of water through injured BBB may be achieved. In this way one can minimize the formation of extracellular oedema (Grände et al., 1997b, 2002, Nordström et al., 2003). Thus, the treatment algorithm of ICP targeted therapy can be responsible for the absence of association between CPP and MAP with DC. There was an association with S100B with the DC group at all time-points including bulk release and maximal release concentration. On the contrary, only initial and maximal NSE was associated with DC. These findings agrees with a previous report that suggests the NSE response is due to mechanical disruption and structural degeneration of neuronal tissue and S100B reflects active secretion due to on-going damage (Herrmann et al., 2000). The DC group was characterized by on-going release of S100B suggesting continuous evolution of pathological changes, justifying the decision to surgically decompress the brain.

**DC and outcome**

In our treatment protocol of sTBI, DC is the last step, and should be used to
treat only the most traumatized patients who do not respond to either medical and/or surgical treatment. In the present material almost 40% of the DCs were performed during the initial evacuation of the haematoma due to the massive cerebral oedema. The DC group had worse ISS, APACHE II and Rotterdam score. Furthermore, the patients had general lower GCS (albeit not statistical significant) and higher levels of S100B and NSE than the NDC group. Therefore, it is not surprising that the outcome in the DC group, presented as GOSE at six months, was worse than the outcome in the NDC group, results that are similar to a previous presented by a randomized clinical trial on the effects of DC (DECRA) (Cooper et al., 2011). However, we believe that the higher morbidity and mortality in the DC group does not disqualify DC as a part of a treatment protocol. The DECRA protocol defines refractory ICP as ICP above 20 mmHg for longer than 15 minutes, justifying the DC procedure. According to our view, this definition does not identify potential candidates for DC. Furthermore, patients with elevated ICP due to the intracranial haematomas were excluded according to DECRA protocol. Finally, patients were treated with bifrontal DC, a procedure more applicable for treatment of diffuse cerebral oedema rather than focal hemispheric swelling with midline shift, the condition of most of our patients. According to our protocol, DC was performed as a life saving procedure in patients with established ICP >25 mmHg impossible to control by any other measure. This characteristic accounts for the 43.7% of mortality in the DC group but only 15% mortality in the total studied group. Nevertheless, it is crucial to understand the associated risks of this procedure. Our results also indicate that Rotterdam score on CTi, ICP_{max\ day1} and S-100B are prognostic factors for
the need of DC and Rotterdam was the strongest predictive factor in the model.

**DC and cranioplasty**

Since DC inevitably leads to a cranioplasty, the results of cranioplasty by itself contribute to the final outcome of the patients with sTBI treated with DC. We found a high complication rate (41%) as the result of cranioplasty. This rate is slightly higher (36.5%) than reported by Zanaty et al. (Zanaty et al, 2015). Univariate analysis revealed that the chosen material was the only variable associated with complications. Time to cranioplasty was close to the statistically significance, indicating higher risk of re-operation with the longer time passed after DC. The infection rate in our material was within acceptable levels (10%). In the literature rate of infection associated with cranioplasty ranges from 0% to 21.4%. As with the meta-analysis reported by Yadla et al., we could not find any statistical difference between the material groups regarding infection rate (Yadla et al., 2011). Contamination during implantation can be responsible for bone graft infection rate (Prolo et al., 1979, Ono et al., 1993). However, because bacteria can survive long freezing times and still retain the capacity to grow, bone grafts should be autoclaved before freezing (Osawa et al., 1990).

The timing of cranioplasty remains controversial. The cranioplasty in our material was performed at about four months after DC. Several publications demonstrate favourable results with early cranioplasty. The argument for an early cranioplasty is that the extended decompression time accumulates the
negative affect of atmospheric pressure on the cerebral perfusion, changes the hydrodynamics of CSF and inhibits rehabilitation (Moreira-Gonzalez et al., 2003, Beauchamp, et al., 2010, Bender et al., 2013). However, other studies have found that early cranioplasty results in a higher risk for infection and general higher complication rate (Gooch et al., 2009, Schuss et al., 2012). The latest studies including a meta-analysis suggest no statistical difference in surgical timing (Sobani et al., 2011, Yadla et al., 2011).

Autologous bone is considered the best material for cranioplasty in terms of cost-effectiveness, infection risk, tissue compatibility and cosmetic results (Bruce et al., 2003, Jankowitz et al., 2006, Beauchamp et al., 2010). However, the vast majority of the complications in our material occurred in the autologous bone group due to post-operative haematoma 20% and bone flap resorption 20%. Post-operative haematoma is a well known complication (Broughton et al., 2014, Zanaty et al., 2015). It is possible that haematoma collection is a result of diffuse oozing from bone edges and dura mater after a necessary dissection that requires fitting an autologous bone flap correctly. This is important in order to facilitate osteoconduction and minimise bone resorption (DeLacure et al., 1994, Moreira-Gonzalez et al., 2003). The reported occurrence of autologous bone resorption ranges between 2% and 50% (Iwama, et al., 2003, Grant et al., 2004, Grossman et al., 2007). Replaced bone graft is incorporated in a complex process of remodelling, which starts with resorption followed by creeping substitution (Prolo et al., 1979). Revascularisation and osteoblasts infiltration appear from edges of surrounding viable bone inwards of the bone graft. The bone
flap serves as an anatomical template or scaffolding for invading of osteoinductive cells (Movassaghi et al., 2006). It has been shown that osteocytes and structural proteins inside the bone flap remain intact during cryopreservation (Prolo et al., 1979). Boiling or autoclaving of bone graft denaturates bone proteins and impair vascularisation, which can lead to resorption (Odom et al., 1952, Abbott et al., 1953). On the contrary PMMA is described as responsible for seroma collection due to exothermic reaction that occurs after moulding (Blum et al., 1997). We did not experience this in our material. This could be due to the technique used with vigorous flushing with cold saline during the procedure.

A large size of the craniectomy and VP shunts are recognized as risk factors for bone graft resorption. Similar to Grand et al., we were unable to verify the association between these factors and incidence of resorption (Grant et al., 2004). However, resorption of the graft is responsible for the longer mean survival time of the implant in PMMA group. Our results suggest that the allograft transplant should be the first choice material for the cranioplasty. Moreover, the planning of cranioplasty should be initiated directly after performing the DC. The rapid development of 3D digital design and 3D printers opens up the possibility of a whole scale of tailored implants that fulfil cosmetic demands with low cost and almost no risks of resorption/dislodgment. This, however, must be validated by prospective, randomized trails.
“Men occasionally stumble over the truth, but most of them pick themselves up and hurry off as if nothing ever happened.”

— Winston S. Churchill
Conclusions

The treatment of severe head injury remains a challenging task. Use of CT classification systems, ICP / CPP measurement and biochemical biomarkers might help to predict the development of secondary pathological changes and the clinical outcome. Used in combination, these classifications allow the treating physicians to predict the need for decompressive craniectomy, reducing the number of "prophylactic" DCs. This reduction is especially important, as cranioplasty following DC is associated with a high rate of complications. We believe that our results might help clinicians to better evaluate patients with sTBI and reduce morbidity and mortality.
“La vie c’est comme la bicyclette: quand on arrête de pédaler on tombe.”

— Albert Einstein
Thesis summary

The dynamic of changes that occur after an sTBI is still not fully understood. The initial cerebral trauma initiates a complex chain-reaction of pathological changes involving inflammatory, metabolic, biochemical, and even hormonal events, the secondary insults.

The goal of the treatment after sTBI is to prevent and minimize the development of secondary insults before irreversible damage to cerebral tissue occurs. The primary measures are to prevent the development of reactions resulting in high ICP and eventually low CPP and thus aggravating the spread of the cerebral ischemia. According to the treatment protocol, the patients with sTBI are sedated, intubated and mechanically ventilated. This requirement, however, limits the clinical neurological evaluation. The analysis of initial and control CT scans of the brain demonstrates that traumatic changes have their own dynamics. Intraparenchymal haematomas showed a tendency to increase its volume and had a clear negative correlation with clinical outcome. Moreover, cerebral parenchyma that appears “normal” on initial CT scans can become ischemic, swollen or haemorrhagic on control images. Three CT classifications- Marshall, Rotterdam and Morris-Marshall- can be applied for initial CT evaluation. The Rotterdam score and Morris-Marshall classification can be used to describe the deterioration. Rotterdam score seems to be the most suitable classification system and can be used to predict the deterioration of pathological changes and forecast clinical outcome.
The value of CT classifications, which describe the extend of cerebral injury and dynamics deterioration due to secondary insults, is reflected in its correlation to biochemical biomarker levels (S100B and NSE) as well as maximal values of ICP and minimal values of CPP. The combination of CT classifications together with the level of biomarkers measured in blood improves clinical forecasting. The patients, who despite maximal treatment develop therapy resistant intracranial hypertension, can require treatment with DC. This life-saving surgical procedure is the last resort in the treatment protocol. During the DC, large portions of the cranium are removed and the dura is opened very wide in order to create the space for the swollen, traumatized brain to expand.

There is an association between the levels of S100B, NSE, Rotterdam classification and DC. Observation and quantifying of these changes can be used to predict the intracranial pathological progression with subsequent refractive intracranial hypertension.

The patients who undergo DC require later a cranioplasty. During this procedure, either the patient’s own skull bone is re-implanted or is replaced by a bone substitute. This surgical procedure is associated with a high incidence of postoperative complications. The use of the patient’s own skull bone is associated with a higher complication rate than PMMA so this must be taken into account when considering DC. Use of CT classifications, ICP / CPP measurement and biochemical biomarkers might help to predict the development of secondary pathological changes. These three strategies would be particularly important as a clinical tool that supports the prediction
of the clinical outcome and isolates the patients in need of DC before irreversible changes are apparent on CT scans. Moreover, this approach would restrict a number of "prophylactic" DCs and decrease the risk of accompanied cranioplasty.

**Sammanfattning på svenska**

De dynamiska förändringarna som uppstår intrakraniellt i samband med och efter en svår skallskada är fortfarande inte helt klarlagda. Efter det initiala traumat startar en våg av patologiska förändringar av inflammatorisk-, metabol-, biokemisk- och även hormonell typ. Denna kaskad av förändringar, vilka har negativt inflytande på varandra, är varken helt förstådda eller lätta att behandla och förebygga. Målet med den primära behandlingen vid en svår skallskada är att förhindra och minimera utvecklingen av s.k sekundära intrakraniella skador. De viktigaste primära åtgärderna är att förebygga utbredning av ischemin genom att sänka ICP. Det är oerhört viktigt att i god tid kunna upptäcka kaskaden av sekundära förändringar innan irreversibla skador uppstår.

Hos patienter med svår skallskada, som trots behandling, utvecklar stigande och behandlingsrefraktärt ICP, genomförs dekompressiv kraniektomi (DK). Här avlägsnas stora delar av skalltaket, och den härda hjärnhinnan (dura mater) öppnas, med avsikten att avbryta ICP-stegringen. Patienterna kommer senare att vara i behov av en ytterligare operation, kranioplastik, under vilken antingen patientens eget skallben sätts tillbaka eller ersätts med ett bensubstitut.

En fråga i delarbete tre var om man med hjälp av dessa parametrar kan förutspå den patologiska kaskaden som orsakar terapiresistent intrakraniell hypertoni. Patienter som utvecklar detta behandlas med DK. Vi kunde påvisa en signifikant association mellan S100B, maximalt ICP, Rotterdam klassifikation och genomgången DK. Dessa parametrar kan alltså användas
“I'm a man of simple tastes. I'm always satisfied with the best.”

— Oscar Wilde
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L'enfer, c'est les autres - Jean-Paul Sartre
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