Secondary Insults in Neurointensive Care of Patients with Traumatic Brain Injury

KRISTIN ELF
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Abstract

Traumatic brain injury (TBI) is a major cause of death and disability. Intracranial secondary insults (e.g. intracranial haematoma, brain oedema) and systemic secondary insults (e.g. hypotension, hypoxaemia, hyperthermia) lead to secondary brain injury and affect outcome adversely. In order to minimise secondary insults and to improve outcome in TBI-patients, a secondary insult program and standardised neurointensive care (NIC) was implemented. The aim of this thesis was to describe patient outcome and to explore the occurrence and prognostic value of secondary insults after the implementation.

Favourable outcome was achieved in 79% and 6% died of the 154 adult TBI patients treated in the NIC unit 1996-97. In an earlier patient series from the department, 48% made a favourable outcome and 31% died. Hence, the outcome seems to have improved when NIC was standardised and dedicated to avoiding secondary insults.

Secondary insults counted manually from hourly recordings on surveillance charts did not hold any independent prognostic information. When utilising a computerised system, which enables minute-by-minute data collection, the proportion of monitoring time with systolic blood pressure > 160 mm Hg decreased the odds of favourable outcome independent of admission variables (odds ratio 0.66). Hyperthermia was related to unfavourable outcome. Hypertension was correlated to hyperthermia and may be a part of a hyperdynamic state aggravating brain oedema.

Increased proportion of monitoring time with cerebral perfusion pressure (CPP) < 60 mm Hg increased the odds of favourable outcome (odds ratio 1.59) in patients treated according to an intracranial pressure (ICP)-oriented protocol (Uppsala). In patients given a CPP-oriented treatment (Edinburgh), CPP <60 mm Hg was coupled to an unfavourable outcome. It was shown that pressure passive patients seem to benefit from an ICP-oriented protocol and pressure active patients from a CPP-oriented protocol. The overall outcome would improve if patients were given a treatment fit for their condition.

Keywords: Traumatic brain injury, Neurointensive care, Monitoring, Secondary insults, Intracranial pressure, Cerebral perfusion pressure, Pressure reactivity, Temperature, Neural network, Outcome

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Till Johan
I. Outcome after traumatic brain injury improved by an organized secondary insult program and standardized care
Kristin Elf, Pelle Nilsson and Per Enblad

II. Prevention of secondary insults in neurointensive care of traumatic brain injury
Kristin Elf, Pelle Nilsson and Per Enblad

III. Cerebral perfusion pressure between 50-60 mm Hg may be beneficial in head injured patients – A computerised secondary insult monitoring study
Kristin Elf, Pelle Nilsson, Elisabeth Ronne-Engström, Tim Howells and Per Enblad
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IV. Pressure reactivity as a guide in the treatment of cerebral perfusion pressure in patients with brain trauma
Tim Howells, Kristin Elf, Patricia Jones, Elisabeth Ronne-Engström, Ian Piper, Pelle Nilsson, Peter Andrews and Per Enblad

V. Temperature disturbances in traumatic brain injury – Relationship to secondary insults, barbiturate treatment and outcome
Kristin Elf, Pelle Nilsson, Elisabeth Ronne-Engström, Tim Howells and Per Enblad
Submitted
CONTENTS

Abbreviations........................................................................................................... vii

1. Review of Traumatic Brain Injury ....................................................................9
   1.1 History ........................................................................................................ 9
   1.2 Epidemiology ............................................................................................ 9
   1.3 Introduction to Avoidable factors/Secondary insults ............................... 10
      1.3.1 Pre-admission avoidable factors and talk and die cases .................. 10
      1.3.2 Avoidable factors/secondary insults during hospital care ............. 11
   1.4 Neurointensive care .................................................................................. 11
   1.5 Brain injury mechanisms ......................................................................... 11
      1.5.1 Concept of primary and secondary brain injury ......................... 11
      1.5.2 Ischaemia ........................................................................................ 12
      1.5.3 Blood flow, threshold levels and autoregulation .......................... 12
      1.5.4 Excitotoxicity ............................................................................... 15
      1.5.5 Reactive free radicals .................................................................. 16
      1.5.6 Inflammatory response ................................................................ 17
   1.6 Clinical drug trials ................................................................................... 17
   1.7 Secondary insults ...................................................................................... 18
      1.7.1 Intracranial hypertension .............................................................. 18
      1.7.2 Cerebral perfusion pressure .......................................................... 20
      1.7.3 Blood pressure ............................................................................... 21
      1.7.4 Hypoxaemia, cerebral hypoxia and hypercapnia ......................... 21
      1.7.5 Temperature .................................................................................. 22
      1.7.6 Glucose ......................................................................................... 24

2. Aims .................................................................................................................. 26
   2.1 General aim .............................................................................................. 26
   2.2 Specific aims ............................................................................................ 26

3. Methods .......................................................................................................... 27
   3.1 The secondary insult program and TBI management protocols ............ 27
      3.1.1 The NIC secondary insult program .............................................. 27
      3.1.2 The standardised NIC treatment protocol system ...................... 27
      3.1.3 TBI management protocols ....................................................... 27
   3.2 Patient selection ....................................................................................... 30
   3.3 Demographic data .................................................................................... 30
# Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>AIS</td>
<td>Abbreviated Injury Scale</td>
</tr>
<tr>
<td>AMPA</td>
<td>$\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionate</td>
</tr>
<tr>
<td>ARDS</td>
<td>Adult respiratory distress syndrome</td>
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<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
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<tr>
<td>BBB</td>
<td>Blood brain barrier</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>BPm</td>
<td>Mean blood pressure</td>
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<tr>
<td>BPs</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
</tr>
<tr>
<td>CBV</td>
<td>Cerebral blood volume</td>
</tr>
<tr>
<td>CEO2</td>
<td>Cerebral extraction of oxygen</td>
</tr>
<tr>
<td>CPP</td>
<td>Cerebral perfusion pressure</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computerised tomography</td>
</tr>
<tr>
<td>D</td>
<td>Dead</td>
</tr>
<tr>
<td>DALYs</td>
<td>Disability adjusted life years</td>
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<tr>
<td>GCS</td>
<td>Glasgow coma scale</td>
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<tr>
<td>GCS M</td>
<td>Glasgow coma scale motor score</td>
</tr>
<tr>
<td>GMT</td>
<td>Good monitoring time</td>
</tr>
<tr>
<td>GOS</td>
<td>Glasgow outcome scale</td>
</tr>
<tr>
<td>GOSE</td>
<td>Glasgow outcome scale extended</td>
</tr>
<tr>
<td>GR</td>
<td>Good recovery</td>
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<tr>
<td>HRT</td>
<td>Heart rate</td>
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<tr>
<td>ICP</td>
<td>Intracranial pressure</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>ISS</td>
<td>Injury severity score</td>
</tr>
<tr>
<td>MD</td>
<td>Moderate disability</td>
</tr>
<tr>
<td>NIC</td>
<td>Neurointensive care</td>
</tr>
<tr>
<td>NICU</td>
<td>Neurointensive care unit</td>
</tr>
<tr>
<td>NISS</td>
<td>New injury severity score</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NO</td>
<td>Nitrogen oxide</td>
</tr>
<tr>
<td>NOS</td>
<td>Nitrogen oxide synthase</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PMNs</td>
<td>Polymorphonuclear leukocytes</td>
</tr>
<tr>
<td>PRx</td>
<td>Pressure reactivity index</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
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<tr>
<td>PTH</td>
<td>Posttraumatic hyperthermia</td>
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<tr>
<td>PtO₂</td>
<td>Brain tissue oxygenation tension</td>
</tr>
<tr>
<td>PVI</td>
<td>Pressure volume index</td>
</tr>
<tr>
<td>RLS</td>
<td>Reaction level scale</td>
</tr>
<tr>
<td>RNS</td>
<td>Radical nitrogen species</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver operating characteristic</td>
</tr>
<tr>
<td>ROS</td>
<td>Radical oxygen species</td>
</tr>
<tr>
<td>SD</td>
<td>Severe disability</td>
</tr>
<tr>
<td>SI</td>
<td>Secondary insult</td>
</tr>
<tr>
<td>SjvO₂</td>
<td>Oxygen saturation of jugular vein</td>
</tr>
<tr>
<td>TBI</td>
<td>Traumatic brain injury</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumour necrosis factor</td>
</tr>
<tr>
<td>TRISS</td>
<td>Trauma score and injury severity score</td>
</tr>
<tr>
<td>VS</td>
<td>Vegetative state</td>
</tr>
<tr>
<td>XO</td>
<td>Xanthine oxidase</td>
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1. REVIEW OF TRAUMATIC BRAIN INJURY

1.1 History

Head trauma has long been considered a serious condition that is often followed by impairment or death. Homer noted 700 BC that close to 100% of combatants with head injuries died (45). Trepanation of the skull was performed in several ancient cultures, but the procedure was mainly carried out in healthy people and not as decompressive surgery of intracranial expansions (66). During the 20th century, it became possible to salvage patients with life threatening head trauma due to both the development of trepanation and other more complicated operations and the development of antibiotics.

1.2 Epidemiology

The reported incidence of traumatic brain injury (TBI) varies due to the definition of diagnosis, time-period studied and country. Population-based studies in the United States suggest an incidence of 180-250 per 100,000 people per year. In Australia, the incidence of TBI was 100 per 100,000 in 1988 and in Netherlands the TBI incidence was 217 per 100,000 in 1997 (20). In Scandinavia the incidence of TBI requiring hospital care has been reported to be approximately 200 per 100,000 in one year (151). The incidence of head trauma in Sweden 1996 was 235 per 100,000 (178, 182). About 10% of TBI cases can be regarded as severe (20).

The incidence of TBI peaks in adolescents and young adults in most patient series (20) but in a prospective population based study from France, the highest incidence was found in the elderly (≥ 75 years) (114). In the latter study, the median age was 44 years. Men are at a higher risk of TBI than women with a male-to-female ratio of about 2:1 (20). Generally, road traffic accidents are the most common cause of TBI followed by falling (20, 179); however, in children and the elderly falling is the most common cause (20). TBI caused by traffic accidents seem to decline resulting in increased pro-
portions of other causes, e.g. falls in the elderly (114). In the United States, during the last two decades, deaths caused by TBI after motor vehicle accidents declined 25%, but the TBI-associated deaths due to firearms increased and undermined this effect on the total TBI death rate (179).

In 1996, TBI caused more than 500 deaths in Sweden (48). Apart from death, TBI also causes disability. Olesen and Leonardi measured the burden of brain disease in Europe and found that injuries caused the greatest number of disability adjusted life years (DALYs) (133). Because TBI is common in young people, the TBI-related loss of working years precedes cancer and cardiovascular disease (145). In 1996, the annual expenditure for patients receiving disability pension due to TBI-related problems was 257 million SEK (148). Quality and satisfaction of life are other aspects that are profoundly affected after TBI (115).

1.3 Introduction to Avoidable factors/Secondary insults

1.3.1 Pre-admission avoidable factors and talk and die cases

Already in 1958, Maciver and coll. pointed out that respiratory insufficiency and anoxia contribute to secondary cerebral oedema and death after severe head injury (103). The major breakthrough in the understanding of the impact of secondary insults (SI) on the clinical course of TBI, did not come until almost 20 years later. In the middle 1970’s, Glasgow researchers found that one third of patients who died after admission to a neurosurgical unit had talked at some time after the trauma (152). It was therefore suggested that the primary brain injury was not always the cause of death in patients with TBI. Potentially avoidable complications were found to have caused secondary brain damage, deterioration and death (147, 152). The first avoidable factors to be identified included delays in the treatment of an intracranial haematoma, hypoxia and hypotension (147, 152). Further studies confirmed the prevalence of avoidable factors upon admission to a trauma centre or neurosurgical unit (58, 125). Actions were taken to minimise avoidable factors which lead to secondary brain injury. Haematomas were evacuated more rapidly (120, 164), airway obstruction was avoided by the use of oro-tracheal tubes and mechanical ventilation, and hypotension was managed by treatment of extracranial injuries and liberal administration of intravenous fluids (46, 57, 59, 142).
1.3.2 AVOIDABLE FACTORS/SECONDARY INSULTS DURING HOSPITAL CARE

Despite improvement in initial care, i.e. resuscitation, care during transport and management at a primary hospital, there still remained concerns regarding the in-hospital care. Failure to recognise the development of intracranial haematoma, respiratory problems leading to hypoxia and hypotension were concluded to contribute to death also after hospital admission (74). In Uppsala, Sweden, this led to the development of a neurointensive care unit (NICU), specialised to treat patients with head trauma.

1.4 Neurointensive care

The mission of neurointensive care (NIC) is to protect the injured brain from events that could cause secondary injury and worsen patient outcome. Patients are rigorously monitored to enable early detection of non-normal values and perturbing trends of physiological variables. Early interventions may then avoid secondary insults. The outcome of patients with TBI improved after the establishment of a NICU at Uppsala University Hospital (198).

1.5 Brain injury mechanisms

1.5.1 CONCEPT OF PRIMARY AND SECONDARY BRAIN INJURY

At the moment of trauma, neurons, glial cells and blood vessels are subjected to shearing forces due to rotational acceleration, to compression and distension which are a result of acceleration and deceleration, and to chafing against bony projections on the skull base (119). This causes the primary brain injury.

As a consequence of the primary injury, secondary processes (e.g. blood flow and metabolic disturbances, inflammation, release of excitotoxic amino acids, production of reactive free radicals, disruption of the ion homeostasis, bleedings and oedema development) will be initiated. Those secondary processes may lead to secondary brain injury. Some secondary processes, e.g. bleedings and oedema may appear with clinical signs and symptoms, but some of the secondary processes cannot be seen clinically.
In addition to the primary injury, the brain may also be subjected to SI, e.g. systemic hypotension, hypoxia, increased ICP due to intracranial haematoma or oedema, and hyperthermia. Those secondary clinical events, sometimes called avoidable factors (see above) may also lead to secondary brain injury (122, 125). The secondary processes initiated by the primary injury make the brain vulnerable to secondary insults. In addition, the secondary insults potentiate existing and initiate new secondary processes.

1.5.2 ISCHAEMIA

Neuropathological examination of the brains of fatal cases of traumatic brain injury have identified ischaemic damage in 90% of the cases (62, 63). A correlation between ischaemic brain damage and episodes of secondary insults (hypoxia or raised intracranial pressure) has also been demonstrated (62). Secondary insults often cause ischaemia, either by reducing the supply or by increasing the demand of oxygen and substrates.

Cerebral ischaemia arises when the delivery of oxygen and energy substrates falls below the metabolic demands. The normal substrate for the brain is glucose that is metabolised in glycolysis, which yields adenosine triphosphate (ATP) and pyruvate. Pyruvate enters the Krebs cycle where it is utilised to produce more ATP in the presence of oxygen. In the absence of oxygen, the pyruvate is reduced to lactate instead of entering the Krebs cycle. Lactate has recently been shown in vitro also to function as a metabolic substrate for neuronal cells, but it requires oxygen to avoid accumulation (163). This is in accordance with a clinical study by Glenn and coll., indicating that patients with less severe TBI and high cerebral metabolic rate of oxygen could use lactate as an additional fuel source and ultimately have a favourable outcome (61).

1.5.3 BLOOD FLOW, THRESHOLD LEVELS AND AUTOREGULATION

Oxygen and glucose are delivered by the blood. CBF have been estimated to about 52 ml/100g/min for the whole brain in healthy non-ischaemic subjects (201). Astrup and colleagues stated that the critical ischaemic blood flow threshold for electrical/functional disturbance is higher than the threshold for complete electrical failure/infarction (12, 13). This is the foundation for the concept of the ischaemic penumbra – tissue that suffers functional but not structural injury. Further research has shown that a more complex pattern of thresholds with declining flow rate causes progressive disturbances within and between the cells (see review by Hossmann and coll.) (71). Moreover, the risk of development of ischaemic damage not only depends on degree of the
blood flow decrease, but also on the duration (Figure 1) (81). A reversible paralysis occurs when CBF falls below 23 ml/100g/min and infarction when CBF is reduced below 18 ml/100g/min for a few hours (81). In patients with severe TBI, early measurements of CBF correlate with Glasgow coma scale motor score (18). Mean CBF the first 6 hours post trauma has been calculated to 22.5 ml/100g/min and CBF < 18 ml/100g/min, on at least one measurement, occurred in 13% of the patients. Those patients had significantly worse outcome (18).

Figure 1 Duration and severity of decrease in cerebral blood flow (CBF) influence the development of dysfunction and infarction. Figure derived from Jones and coll. (81).

The vessels of the brain can change in diameter in response to metabolism and transmural pressure. This is called the cerebral autoregulation (139). The energy substrates and the oxygen delivery to the brain is thereby maintained during different physiological conditions and adjusted according to the regional needs. Apart from this, the cerebral vessels can change their calibre and thereby cerebral blood flow (CBF) due to changes in PaCO₂ (perivascular pH) (134) and PaO₂ (117). This mechanism is passive and is usually not counted as a part of autoregulation.

The part of autoregulation where the tone of the smooth muscles in the arterial wall changes in response to changes in transmural pressure, is called cerebrovascular pressure reactivity, or pressure autoregulation. This is the mechanism of autoregulation that enables a constant blood flow between mean blood pressures of 60-150 mm Hg (139) in healthy subjects (Figure 2). After head trauma, autoregulation has been assessed to be impaired in 50% of the patients (54). In earlier studies on autoregulation, it was found that...
autoregulation was disturbed 36 hours after trauma (54). More recent re-
search has shown a more complex pattern, where the autoregulatory re-
sponse may change over time within the patients (95). Further, measure-
ments on CO₂ reactivity have shown different degrees of reactivity in differ-
ent parts of the brain after trauma (104), which is also likely to be true for
pressure autoregulation.

![Figure 2: Cerebral blood flow (CBF) in response to mean blood pressure (BPm).](image)

Lang and coll. observed three intracranial pressure (ICP) response types to
blood pressure (BP) manipulations (95):

- **Pressure passive** – lowering BP produces a decrease in ICP and/or rais-
ing of BP produces an increase in ICP.
- **Pressure stable** – little or no ICP response to manipulation of BP.
- **Pressure active** – lowering BP produces an increase in ICP and/or raising
  of BP produces a decrease in ICP.

When the pressure passive response is seen, the pressure autoregulation is
impaired and vessels lose their ability to constrict with increasing BP and
dilate in response to decreasing BP; thus a change in BP is passively trans-
mitted to the ICP. This response can be seen in patients in whom the auto-
regulation is impaired due to injury, but also in patients with preserved auto-
regulation when the BP is very low or very high (outside autoregulatory
range). The pressure active response reflects a state with preserved pressure
autoregulation within the autoregulatory BP span. A decrease in BP is fol-
lowed by vasodilatation, which increases the blood volume in the skull and
thus increases the ICP; contrastingly, when an increase in BP is followed by
vasoconstriction, intracranial blood volume is decreased and thereby a de-
crease in the ICP results. The pressure stable response means that the ICP
does not change due to BP changes. The pressure stable response would be the result when the compliance (see page 19) is high and is most likely to be seen in patients with preserved autoregulation. The responses of ICP and CBF to changes in BP are illustrated in Figure 3.

Figure 3 Cerebral blood flow (CBF) and intracranial pressure (ICP) in relationship to blood pressure (BP) with preserved and impaired autoregulation. The rings at the top represent the change in blood vessel diameter in the different situations.

1.5.4 EXCITOTOXICITY

Glutamate is the main excitatory amino acid in the brain (52). The glutamate stimulation of the postsynaptic ligand-gated ion channel receptors (NMDA, AMPA and Kainate) is normally transient, but if prolonged, the neuron will die. This is called excitotoxicity. Elevated levels of glutamate have been measured with microdialysis in patients with TBI (22, 68, 200). High glutamate has been associated with high ICP and other ischaemic insults (such as hypotension and hypoxaemia), as well as with unfavourable outcome (22, 92).

There are several possible mechanisms that can lead to increased glutamate stimulation and excitotoxicity. The interstitial glutamate concentration is considerably lower than the concentration in the blood or within the cells. Leakage from damaged cells or a disrupted blood brain barrier (BBB) may
cause glutamate concentrations at toxic levels. The glutamate uptake system is very effective but uses energy derived from the sodium gradient across the membrane, and in the situation of energy depletion, e.g. ischaemia, the glutamate transport may be impaired or even reversed. When energy is exhausted the Na⁺/K⁺ -ATPase activity diminishes and except from impaired glutamate transport, there will be an influx of sodium, chloride and water into the cell. This cell swelling may in turn cause further release of glutamate (98).

The toxic effect of glutamate may be divided into two components. The first includes sodium influx followed by chloride and water influx and neuronal swelling. The second component includes excessive calcium influx (29). Calcium may then trigger a series of reactions by activation of several proteins. Activation of protein C leads to alterations in the membrane calcium channels that further enhances calcium influx. Calcium also activates Calpain I, a protease that degrades neuronal structural proteins. Further, calcium activates phospholipase, xantine oxidase (derived from xantine dehydrogenase catalysed by a calcium activated protease) and nitric oxide synthase. These enzymes produce free oxygen radicals that trigger peroxidative degradation. For review see (30, 172).

1.5.5 REACTIVE FREE RADICALS

Reactive free radicals are molecules that have at least one unpaired electron. In TBI, reactive oxygen species (ROS) and reactive nitrogen species (RNS) have been studied. These molecules are produced in small amounts in normal cell processes, e.g. during oxidative metabolism in the mitochondria. Nitrogen oxide (NO), which normally acts as a smooth muscle relaxant factor in the vessels, is also a free radical produced by nitrogen oxide synthase (NOS) (137). Other ROS have also been shown to modulate the tone of vasculature (157). Endogenous defence mechanisms, so called antioxidants, including enzymes e.g. superoxide dismutase and glutathione peroxidase and low-molecular weight antioxidants e.g. ascorbic acid and tocopherol, neutralise the radicals. It has been suggested that there is a correlation with the degree of antioxidant response and clinical recovery (169).

After TBI, free radicals are produced superfluously by several mechanisms. Excitotoxicity caused by excessive glutamate stimulation increases intracellular calcium which activates enzymes that form free radicals: xantine oxidase (XO), NOS and phospholipase (30, 172). Excitotoxicity also leads to calcium influx into the mitochondria, which causes structural alterations of the inner mitochondrial membrane with disorganisation of the electron transport chain, which may increase ROS formation (93, 97). Acidosis en-
hances free radical formation, possibly because the low pH releases iron from transferrin and ferritin, which then catalyses the production of free radicals (170). Another source of free radicals is inflammatory cells (14).

Free radicals cause lipid peroxidation. The following conformational changes of the membranes lead to loss of membrane functional integrity (67). It has been suggested that free radicals damage endothelial cells of the BBB (24); furthermore, scavengers of reactive free radicals have been shown to decrease BBB permeability and brain oedema (106, 118). Free radicals may also oxidise proteins and DNA (116, 135, 206) and cells exposed to $\text{H}_2\text{O}_2$ either undergo apoptosis or necrosis depending on the concentration of $\text{H}_2\text{O}_2$ (55).

1.5.6 INFLAMMATORY RESPONSE

Complement components have been found in the penumbra of cortical contusions in human brain as early as 2.5 hours after trauma (16). Pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-$\alpha$) are produced in the injured brain within hours after trauma (69, 187). TNF-$\alpha$ induces BBB-disruption (193), but the cytokines primarily induce an inflammatory response by acting as chemoattractants to leukocytes. Neutrophils have been found lining the vasculature of and injured cortex two hours after injury. The infiltration into the parenchyma peaks at about 24-48 hours after trauma and 24 hours post-trauma macrophages can also be found in the injured area (177). The mononuclear cell response is evident on day two and has a maximum 5-6 days post trauma (70). The leukocytes release enzymes, free radicals and vasoactive mediators, which alter cerebral vasoreactivity. The accumulation of polymorphonuclear leukocytes (PMNs) have been shown to correlate with brain oedema formation after brain injury (162).

1.6 Clinical drug trials

With the growing body of knowledge of presumptive mechanisms causing brain injury, great effort has been put into the development of neuroprotective drugs. Glutamate antagonists, free radical scavengers, calcium antagonist, bradykinin antagonist, steroids and anticonvulsants have been investigated, but none has yet proved beneficial in phase III trials. Despite promising pre-clinical data, most trials have failed to demonstrate any significant improvement in outcome (129). From this point of view, improvements in the clinical care of the patients seem to be of even greater importance.
1.7 Secondary insults

1.7.1 Intracranial Hypertension

In the original article about patients who talk and die by Reilly and colleagues, the observance for raised ICP is annotated (147). The authors suggest clinical observation of the conscious level to discover intracranial haematoma, diffuse swelling or other causes for raised ICP. Still, regular assessment of the conscious level using either the Reaction Level Scale (RLS) (181) or Glasgow Coma Scale (GCS) (189) together with continuous measurement of ICP and computerised tomography (CT) scanning are the foundation of discovering expansive processes.

ICP can be measured via an intraventricular catheter or by an intraparenchymatous probe. Non-invasive methods to measure ICP have been developed (161), but none is yet in clinical use for TBI patients. The intraventricular drainage system gives, in favour of the intraparenchymatous probe, the possibility to drain liquor, thereby decreasing intracranial pressure. It is regarded as the golden standard for ICP monitoring (108). When the ventricles are collapsed, the intraventricular drainage system cannot be used and the intraparenchymatous probe is preferred. It is usually assumed that the brain acts like a fluid and thus the ICP is transmitted equally throughout the intracranial space. Some studies imply that this is not always the case and that the pressure is significantly higher close to an extracerebral mass lesion (23, 205).

In healthy humans, the ICP is 2-7 mm Hg (101). A rise in ICP is caused by increases of intracranial subvolumes, e.g. increased amount of cerebrospinal fluid (CSF), increased cerebral blood volume (CBV) or increased brain volume. After trauma, an increase in CBV may be caused by vasodilatation or by space occupying lesions e.g. epidural, subdural or intraparenchymatous haematomas. Increased brain volume is due to brain oedema, which is often divided into cytotoxic (intracellular) oedema and interstitial oedema. The cytotoxic oedema is caused by changes in the ion homeostasis with cellular influx of sodium and efflux of potassium during ischaemia (87). Acidosis and glutamate release increase the entry of sodium into the cells, thereby causing them to swell as water follows the sodium (29, 86). The interstitial oedema is likely to be caused by vascular engorgement and disruption of the blood brain barrier. Leakage of molecules into the interstitium increases the osmotic pressure which together with the hydrostatic transcapillary pressure causes water to enter the interstitium (9, 65). Disturbances in the CSF dynamics may cause hydrocephalus and raised ICP.
Figure 4 demonstrates the ICP response to added intracranial volume. Initially, the intracranial compartments can compensate for the added volume, but when the compensatory abilities are exhausted, ICP increases exponentially (100). The increase in ICP per increase in volume, dP/dV, is called the intracranial elastance, and the volume needed to increase the pressure a certain amount is called the intracranial compliance (124). The compliance follows a hyperbole curve and is sometimes presented as the pressure volume index (PVI). PVI denotes the volume needed to change the log ICP with 1 unit, i.e. to achieve a tenfold increase in ICP (109). The PVI in non-traumatised adults has been estimated to about 26 ± 4 mm Hg (166). Patients with the same ICP may have differing compliances, and patients with decreased compliance seem to require more aggressive treatment and also have a poorer outcome (113). Recently, it has become possible to continuously monitor the compliance in patients (144, 207, 208), although it has not yet been implemented as a tool in the daily care.

The Swedish neurosurgeon Nils Lundberg did important pioneer work on the continuous monitoring of ICP in patients and in diagnosing and treating a variety of intracranial disorders (101). He described three basic ICP waveforms: A, B and C waveforms. The most important of the three, the A wave, also called the plateau wave, was found to herald uncontrollable ICP. A-waves are characterised by a steep rise in ICP to 50 mm Hg or more, followed by a plateau at that level for 2-15 minutes, thereafter the ICP suddenly falls to a level slightly above the initial level. The B- and C-waves both are suggestive but not pathognomonic of increased ICP. Their amplitudes are smaller and their durations are shorter than the A-waves (101). Together with the analogue ICP waveform registration, the ICP is now monitored digitally minute by minute. The prognostic value of ICP patterns shown this way is yet to be studied.
The detrimental effect of raised ICP is well documented (80, 107, 122, 123, 173, 199). High ICP impairs the circulation and contributes to ischaemic damage. It also bears a risk of brain herniation and compression of the brain stem, especially if there is an infratentorial, temporal or temporoparietal mass lesion (6, 111). The treatment of intracranial hypertension is dependent on the cause. Removal of intracranial haematoma without delay is of great importance (120, 164). Contusions can also be removed surgically. When there is no surgically available cause of ICP rise, mild hyperventilation, sedation or CSF drainage may be used. In cases of persisting high ICP in spite of standard treatment, barbiturate coma is an alternative (49). Barbiturate treatment reduces oxygen metabolism and CBF (83) which reduces ICP. Opinions of the beneficial effects of barbiturate treatment differ since barbiturates have serious side effects, e.g. infections, cardiovascular impairment and electrolyte disturbances, that have to be considered (160). Another option to treat intractable high ICP is to perform decompressive craniectomy (removal of the skull bone).

1.7.2 CEREBRAL PERFUSION PRESSURE

Cerebral perfusion pressure (CPP) is calculated as the difference between mean arterial pressure (BPm) and ICP; \( BPm = \frac{BP_{systolic} + 2 \times BP_{diastolic}}{3} \). It is used as a crude measure of the CBF. Since ischaemia can be caused by too low CBF, low CPP has been considered a dangerous secondary insult. Keeping CPP at a level of at least 70 mm Hg has been thought to ensure sufficient blood flow and thereby reduce the risk of ischaemia and intracellular oedema (26, 73, 153). The American TBI guidelines recommends CPP to be kept > 70 mm Hg (21); however, levels as high as 90-100 mm Hg have also been suggested (153, 154). Vasopressors are then used to artificially raise BP/CPP. The theory behind this strategy is that a moderately elevated ICP can be tolerated as long as the CPP is at least 70 mm Hg, which would guarantee a satisfactory cerebral blood flow. In patients with preserved autoregulation, the ICP may decrease due to vasoconstriction when the BP increases.

Other researchers have focused on the formation of interstitial oedema. Opening of the BBB, in combination with impaired autoregulation, is thought to induce transcapillary fluid filtration (64). A treatment protocol thought to reduce brain oedema and ICP, including hypotensive treatment (\( \beta_1 \)-blockade and \( \alpha_2 \)-agonist), has been proposed by Lund researchers (10, 11). The optimal CPP management is a matter of controversy. Some researchers have found adverse effects on the outcome of CPP < 60 mm Hg (41), while others state that no protective effect of higher levels of CPP exists (82).
There is only one randomised clinical trial where patients were treated at different CPP levels (≥ 50 mm Hg and ≥ 70 mm Hg) (150). Patients treated with the target CPP of ≥ 70 mm Hg had significantly less desaturation in the jugular vein (SjvO₂) while patients in the lower CPP target group had less refractory intracranial hypertension. The 6-months outcome showed 49.3% favourable outcome in the lower CPP target group and 39.8% favourable outcome in the higher CPP target group (150).

1.7.3 BLOOD PRESSURE

Hypotension (BP_{systolic} < 80-100 mm Hg) was one of the first avoidable factors studied and was often found in patients with extracranial injuries (57, 122, 125, 152). Hypotensive episodes and shock have been shown to independently predict death in TBI patients (26, 107). In an ICU multimodality monitoring study by Jones and coll., hypotensive secondary insult was found to be the most significant predictor of death and poor outcome (80).

There are few recent studies regarding the occurrence and prognostic effect of hypertension in TBI. An excellent review of older works, most of which are still valid has been written by Simard and Bellefleur (175). Jones and coll. defined hypertensive insult as BP_{systolic} ≥ 160 mm Hg or BP_{mean} ≥ 110 mm Hg. In their study, hypertensive insults occurred in 89% of the patients but these did not have a significant effect on neither death/survival nor poor/good outcome (80). This result was repeated by Signorini and coll. – hypertensive insults were common but could not predict outcome (173). A positive correlation between BP and the development vasogenic oedema has been shown in experimental studies (47). Clinical studies have shown that patients who have received vasopressors and fluids to induce hypertension have a greater risk of refractory high ICP (150) and also a fivefold increased risk of developing adult respiratory distress syndrome (ARDS) (36).

1.7.4 HYPOXÆMIA, CEREBRAL HYPOXIA AND HYPERCAPNIA

Hypoxæmia, the deficient oxygenation of the blood, can be caused by apnoea, airway obstruction, chest- and pulmonary injuries, aspiration, anaemia and later on, pneumonia and ARDS (103, 121). The airway obstruction may be caused by injury, regurgitated objects or by the unconsciousness and inability to maintain muscular tone, causing a collapse of the airway. Miller and coll. reported that upon admission half of the patients with hypoxæmia had extracranial injuries, the other half had isolated head trauma (122, 125). It is of tremendous importance to clear the airway in unconscious patients with head trauma and to use orotracheal tubes and mechanical ventilation.
This was pointed out already in the 1958 by Maciver and coll. (103). Hypoxaemia contributes to ischaemic brain damage and has been shown to increase mortality in TBI patients (80, 122). Further, hypoxaemia causes vasodilatation. When PaO\textsubscript{2} falls below 60 mm Hg (8.0 kPa) CBF increases exponentially (117), which may increase ICP.

The simplest way to measure oxygen saturation in the blood is via a transcutaneous optic measurement with a finger clip adapted to a pulse oximeter. Arterial blood samples are more reliable and provide information regarding PaO\textsubscript{2}, but cannot be used as a continuous monitoring tool. The venous saturation in the jugular bulb (SjvO\textsubscript{2}) has been used as a measure of global cerebral hypoxia and the occurrence of jugular desaturation has been associated with unfavourable outcome when GCS has been controlled for (149). This is thought to reflect a situation of ischaemia where the increased oxygen extraction is caused by relative hypoperfusion. Another way to evaluate the ischaemic status of the brain is through the calculation of the difference of arterio-venous saturation, the cerebral extraction of oxygen (CEO\textsubscript{2}). With this technique a more complex picture has been seen. Initially, high oxygen extraction is associated with a better outcome and low oxygen extraction is associated with a poorer outcome (43). These outcomes suggest that high CEO\textsubscript{2} reflects global cerebral viability, while low CEO\textsubscript{2} may reflect considerable brain damage. Direct measurement of the oxygen tension within the brain tissue, PtiO\textsubscript{2} may be easier to interpret and low PtiO\textsubscript{2} correlates with poor outcome (196); however this technique only reflects the status in the location of the probe and is not a global measure.

Inadequate ventilation also leads to the accumulation of carbon dioxide, CO\textsubscript{2}. The arterial walls of the brain react with dilatation when CO\textsubscript{2} increases. The blood volume in the skull increases as well as the ICP. Hyperventilation has long been used as a treatment in TBI patients with the purpose of reducing CBV and ICP. Ventilation that is too aggressive causes potentially harmful vasoconstriction. Brain tissue oxygenation (PtiO\textsubscript{2}) and jugular bulb oxygen saturation (SjvO\textsubscript{2}) decreased when patients were hyperventilated from a PaCO\textsubscript{2} of 29 mm Hg (3.9 kPa) to 21 mm Hg (2.8 kPa) in a study by Unterberg and coll. (195). Prophylactic hyperventilation to a PaCO\textsubscript{2} of 25 mm Hg (3.3 kPa) has been associated with a poorer outcome than non-hyperventilated patients (127). At NIC in Sweden, mild hyperventilation (PaCO\textsubscript{2} 26-35 mm Hg, 3.5-4.6 kPa) has traditionally been used (10, 198).

1.7.5 TEMPERATURE

Body temperature is controlled by the hypothalamus (96). It is kept constant within the range of 36.8-37.2 °C. Vasodilatation and sweating are triggered
when temperature exceeds the upper threshold and vasoconstriction and shivering are triggered when the temperature falls below the lower threshold (211). Temperature disturbances are often seen in patients with TBI. Jere-mitsky and coll., found a mean temperature of 35.6 °C on arrival in 81 severely injured patients (77). Spontaneous hypothermia has been associated with a poorer clinical course and a more unfavourable prognosis than other patients (77, 180). A rise in temperature is often seen in patients after TBI; while the occurrence varies depending on hyperthermic threshold, but at least 50% of patients with TBI experience hyperthermia (4, 89, 184).

There are several causes of hyperthermia. Posttraumatic hyperthermia (PTH) or neurogenic fever, is caused by traumatic injury to the hypothalamus (28), with an incidence of 43% in a post-mortem study (42). In PTH, the injury causes a disruption of the hypothalamic “set point“ temperature, which causes an increase in body temperature (28). The acute phase response to injury includes, among other things hyperthermia, increased synthesis of acute phase proteins (such as C-reactive protein) and increased production of pro-inflammatory cytokines. The acute phase response has been described in TBI patients and lasts for at least three weeks. (209). Infections cause an inflammatory response similar to the acute phase response and results in hyperthermia.

Hyperthermia increases metabolism and thus has been thought to affect the metabolic autoregulation (126), with vasodilatation and an ICP increase as a consequence. Experiments have shown that temperature, independent of metabolism, affects the diameter of blood vessels (132). Generally it has been stated that ICP increases 3-4 mm Hg for every 1°C of temperature elevation (38). Rossi and coll. showed that a rise in temperature was accompanied by a significant rise in ICP and that the ICP declined significantly when fever ebbed (155). Others have also shown that treatment of hyperthermia can cause the ICP to be significantly lowered (39). Further, induced hypothermia has been shown to decrease ICP (78, 105, 191).

Hyperthermia has also been shown to increase the BBB permeability and to cause brain oedema (5, 167). This oedema can be mediated via several mechanisms, including inflammation with polymorphonuclear leukocyte infiltration (25) and increased production of free radicals (88). Hyperthermia may also cause excitotoxic damage due to the increased release of glutamate (2, 186).

Patients that experience hyperthermia during intensive care after TBI are less likely to achieve a favourable outcome (79) and have a higher mortality rate (8). A direct cause and effect relationship has never been shown and pyretic insults have been coupled to both low GCS on admission and infections
during intensive care (184). Induced hypothermia has been used as a treatment in TBI patients. Some studies have shown a better outcome using such therapy (78, 105) whereas others have shown no better prognosis after hypothermic treatment (32).

1.7.6 GLUCOSE

Glucose is the usual energy source for the brain. If the supply of glucose diminishes, the brain can, in the presence of oxygen, utilise ketone bodies (158) or lactate produced by the astrocytes (140, 163). In the absence of oxygen, pyruvate derived from glucose cannot be oxidised in the mitochondrial respiratory chain. Instead, the pyruvate is reduced to lactate with a simultaneous release of H⁺. If the ischaemia is complete, the lactate produced corresponds to the tissue stores of glycogen and glucose (99). If the ischaemia is incomplete the lactate production corresponds positively to the plasma glucose concentrations (i.e. hyperglycaemia increases lactate contents) (85). The relationship between lactate and pH is linear (84). It has been proposed that cell damage caused by acidosis is due to derangement of cell calcium homeostasis (171); however, it is more likely that acidosis enhances the production of free radicals by causing the release of iron and iron-catalysed formation of hydroxyl radicals, which in turn cause lipid peroxidation (170, 171).

Animal experiments have shown higher tissue lactate concentrations, lower brain pH and a poorer recovery of the cortical energy state and EEG patterns in animals given glucose infusion in connection to incomplete brain ischaemia compared with animals not given glucose (110, 146). Histopathological examination of rat brain has shown increased contusion area after fluid-percussion brain injury in hyperglycaemic animals (90) and necrosis resembling ischaemic brain infarction has been observed after injection of lactic acid in the brain (94). Early post injury hyperglycaemia in rats has also been shown to cause neutrophil accumulation in the injured tissue, which may be interpreted as hyperglycaemia induced inflammation (90).

In clinical studies on TBI patients, a relationship between severity of injury measured by GCS and glucose concentrations has been found (156, 210). In a study by Young and coll., patients with glucose concentrations > 200 mg/dl (11.1 mmol/L) had a significantly poorer outcome 18 days, 3 months and 1 year after trauma, compared with patients with lower glucose concentrations, though the independent effect on outcome was not clear (210). In a prospective study by Rovlias and coll., high glucose level (> 200 mg/dl) was associated with a less favourable outcome and postoperative glucose level was an independent predictor of outcome in a multiple analyses (156). Re-
Secondary insults in NIC of patients with TBI

cently, patients in a general intensive care unit where randomised into two groups and treated according to different blood glucose goals, 80-110 mg per decilitre (4.4-6.1 mmol/L) and 180-200 mg/decilitre (10.0-11.1 mmol/L). Patients in the lower blood glucose group had significantly lower mortality and fewer infections. (197). There is no randomised clinical trial performed in TBI patients at this time.
2. AIMS

2.1 General aim

In order to reduce secondary brain injury and improve the clinical outcome after TBI, the general aim was to challenge the secondary insults in the NIC. An organised secondary insult program directed against secondary insults and standardised care had therefore been implemented.

2.2 Specific aims

To evaluate the clinical outcome before and after implementation of the secondary insult program and the standardised regimen protocol system. (Paper I)

To describe the occurrence of secondary insults collected from surveillance charts and to evaluate their independent prognostic value when the NIC was standardised and dedicated to avoid secondary insults. (Paper II)

To install and develop a computerised multimodality monitoring system with the intention to describe the occurrence of secondary insults collected minute-by-minute and to evaluate their independent prognostic value. (Paper III)

To compare the secondary insult patterns during different treatment protocols (ICP-oriented versus CPP-oriented) and to examine the influence on the prognosis of the occurring insults. (Paper IV)

To describe temperature disturbances (hyper- and hypothermia) and relate them to other secondary insults and to the prognosis, taking into account the confounding effect of barbiturate treatment. (Paper V)
3. METHODS

3.1 The secondary insult program and TBI management protocols

3.1.1 THE NIC SECONDARY INSULT PROGRAM

The NIC personnel (nurses and nurse assistants) were educated on the principles of the development of secondary brain damage caused by secondary insults. They were made aware that their main objective was to avoid secondary insults. If an insult could not be corrected efficiently in accordance with the written nursing protocol, the nurse was required to immediately report this to a doctor. Insults were recorded on a special checklist on the surveillance chart and were also reported verbally between the nursing teams and to the doctors during rounds.

3.1.2 THE STANDARDISED NIC TREATMENT PROTOCOL SYSTEM

The standardised treatment protocol system was constructed according to the standards of good medical practice and good laboratory practice. It contained written standardised operative procedures regarding both medical treatment and basic nursing.

3.1.3 TBI MANAGEMENT PROTOCOLS

3.1.3.1 ICP targeted protocol (Uppsala)

The treatment protocol of the SI program was constructed in a stepwise manner, starting with the basal treatment and then escalating to step one and two, if treatment goals could not be accomplished. The standardised treatment algorithm is summarised in Table 1. The NIC management in Uppsala in general followed the core guidelines of the European Brain Injury Consor-
tium (102) and the Brain Trauma Foundation in the United States (21), but
the protocol was more ICP-guided than CPP-guided. The goal was to keep
ICP < 20 mm Hg and CPP around 60 mm Hg. In general, no attempt was
made to increase the CPP to > 60 mm Hg by increasing the blood pressure
above normal levels. In patients who developed increased ICP with high
CPP, the amount of sedation was increased, followed by antihypertensive
treatment if necessary. Vasopressors were used to stabilise systemic pres-
sure, but not to treat CPP.

The principle of keeping CPP around 60 mm Hg without increasing it further
was applied with the idea not to facilitate the development of progressive
brain oedema as in the “Lund concept” (10, 64). Our protocol differed in
some ways from the Lund concept, e.g. CSF drainage was applied earlier
and barbiturate treatment was a later option since the neurological status was
checked regularly to recognise deterioration not preceded by increased ICP
(53) and because barbiturate treatment is potentially dangerous (160, 185).
Furthermore, dihydroergotamine is a central part in the original Lund con-
cept.

3.1.3.2 CPP-targeted protocol (Edinburgh)

In Edinburgh, a more CPP oriented approach was applied. The primary aim
was to achieve a cerebral perfusion pressure of at least 70 mm Hg. Keeping
ICP less than 25 mm Hg was a secondary target. After 24 hours the ICP
treatment threshold was increased to 30 mm Hg. Vasopressors were used to
maintain CPP at 70 mm Hg in the event of persisting elevations of ICP.
**BASAL TREATMENT**

Slightly elevated head
Artificial ventilation in all unconscious patients (GCS M ≤ 5)
Mild hyperventilation (Pa CO₂ 4.0-4.5 kPa)
Opiates as analgesia and Propofol (Diprivan®, Zeneca) as sedation
Fluid substitution to obtain normovolemia with high colloid osmotic pressure
Negative fluid balance and generous infusions of Albumin 20 %
CVP 0-5 mm Hg
Treatment of hypotension
Albumin 20 %
Avoidance of vaspressors
Treatment of combined hypertension and increased intracranial pressure
Metoprolol (Seloken®, Hässéle)
Clonidine (Catapresan®, Boeringer Ingelheim)
Treatment of hyperthermia
Paracetamol (Panodil®, Sterling Health) first choice
Chlorpromazine (Hibernal®, Rhone-Poulenc Rorer) second choice
Cooling blankets third choice
Treatment of hyperglycaemia
Insulin (Actrapid®, Novo nordisk)
Surgical removal of significant mass lesions (> 0.5 cm shift)

**STEP 1 – INCREASED ICP DESPITE BASAL TREATMENT**

Re-evaluation for secondary insults
Development of significant mass lesions
Inadequate sedation
Hypercapnia
Fever
CSF drainage
Initially intermittent drainage
Continuous drainage after 1-2 days against a level of 15-20 mm Hg

**STEP 2 – PERSISTENT INCREASED ICP DESPITE STEP 1**

Re-evaluation for secondary insults
Development of significant mass lesions
Inadequate sedation
Hypercapnia
Fever
Thiopental coma treatment (Pentothal®Natrium, Abbott)
Administered at the lowest dose required to maintain
ICP < 20 mm Hg
Induced hypothermia and hypernatremia considered positive
External decompression/Hemicraniectomy
In case of uncontrollable ICP and tendency to adverse effects of barbiturate treatment
Internal decompression/Lobe ectomy
Exceptionally

**Table 1** Summary of the standardised neurointensive care protocol.
3.2 Patient selection

In papers I and II, patients were emanated from a list of all patients admitted to the NICU with TBI between January 1, 1996 and December 31, 1997. Some patients were excluded due to certain criteria. Children (0-15 years) were excluded because the outcome measurement was not applicable in children (203). Patients 80 years or more were excluded due to the high presence of other diseases. Patients admitted five days after trauma (n = 2) were excluded since the early period is important in the development of secondary insults although insults may occur after this time period as well (194). Patients discharged within 12 hours were also excluded (n = 1). Further, patients with both pupils wide and non-reacting (n = 17) and patients with GCS 3 (n = 1) were excluded because of the expected fatal course (7, 35). One patient with a gunshot injury was also excluded.

In papers III-IV, the same age criteria were used as in the first two papers. Patient selection was then based on monitoring criteria. In papers III and V, 54 hours of valid monitoring data for all physiological variables studied within the first 120 hours after trauma were required. This criterion ensured not only more than two full days of data per patient, but also that the monitoring would start within the third day after trauma. In paper IV, at least 6 hours of data within the first 96 hours were required. These criteria skewed the patient selections toward more severely injured or troublesome patients, thus, the patient series do not represent a random sample.

3.3 Demographic data

3.3.1 Data sources

In papers I and II demographic data were retrieved from patient records. In papers III, IV and V the demographic data were gained from a Microsoft Access 97 database. This database was completed utilising patient records. Data could then be reached via a special software, The Browser, which was also used for analyses and validation of secondary insult data (72, 143). In paper V, analyses of barbiturate concentrations were obtained from records of the Clinical Pharmacology Department.
3.3.2 INJURY SEVERITY CLASSIFICATIONS

3.3.2.1 Degree of consciousness

The level of consciousness soon after trauma is one of the best predictors of outcome and is thought to reflect the primary brain injury. Most common is the Glasgow Coma Scale (GCS) (189). This scale consists of three parts, verbal response, eye response and motor response. The maximum score in a person fully awake with normal speech, spontaneous eye opening and obeying commands, is 15 (5, 4 and 6 points respectively). The lowest possible score is 3, where commands and pain stimulation do not cause the patient to open his eyes, make any verbal sound and no voluntary or reflex movement can be observed. The GCS has been criticised because it is difficult to obtain a full score including all three parts. TBI patients often have facial- or skull base fractures causing haematomas and swelling around the eyes disabling any opening. Further, TBI patients very often require artificial ventilation and hence the orotracheal tube and anaesthesia prevents them from talking. Left to be examined is then only the motor response (Table 2). The motor response allows a good discrimination of patients in coma (motor score 1-5), but it does not separate patients who are alert from patients who are confused or drowsy.

An alternative to the GCS is the Reaction Level Scale (RLS) (181) which is used in Scandinavia. The RLS is an eight-grade single line scale. A patient who is awake and lucid is RLS 1 and a patient who does not respond to commands or to pain stimulation is RLS 8 (Table 2). RLS grades 5-8 correspond to the GCS motor scores (GCS M) 4-1. The RLS score is neither affected by eyelid swelling or haematoma, nor by an orotracheal tube. It discriminates unaffected patients from other non-comatose, but affected patients.

In all five papers we used GCS M since the GCS is internationally accepted. In the clinical practice all patients were assessed according to the RLS scale.
Table 2 Clinical features of the reaction level scale (RLS) and the Glasgow coma scale motor score (GCS M).

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>RLS</th>
<th>GCS M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conscious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alert, oriented</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Drowsy or confused</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Very drowsy or confused, obeys commands</td>
<td>3a</td>
<td>6</td>
</tr>
<tr>
<td>Unconscious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wards off pain</td>
<td>3b</td>
<td>5</td>
</tr>
<tr>
<td>Localises but does not ward off pain</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Withdrawing movement on pain stimulation</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Stereotype flexion movement on pain stimulation</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Stereotype extension movement on pain stimulation</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>No response to pain stimulation</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

3.3.2.2 Neuroradiology

Another way to describe brain injury is by the classification of computerised tomography (CT) scanning. CT scanners are available in all hospitals in Sweden. Fractures, haematomas, contusions and brain swelling can be visualised on the images. Mass lesions, especially subdural haematomas (56), have been associated with a less favourable prognosis than diffuse injuries; furthermore, there is a clear relationship between the degree of midline shift, regardless of type of injury, and mortality (3, 50, 165). Development of intracranial haematomas, contusions and swelling continues hours to days after the trauma. The first CT scan performed in a patient may show a diffuse injury while a second scan reveals a significant mass lesion developed during the time lapsed between the scans (165). Therefore, a repeated CT scan is often motivated, especially if the first CT scan was performed early after trauma. Certain CT scan findings such as the absence of basal cisterns and third ventricle, mass lesion and diffuse injury with large midline shift bear a higher risk of intracranial hypertension (50, 188).

In papers I-III and V the first CT scan performed in each patient was classified according to the Marshall CT classification (Table 3) which is the most common CT classification and has been shown to correlate with outcome (112). It was first used for the analysis of CT scans in the Traumatic Coma Data Bank but has also to a major extent been adopted by the European
Brain Injury Consortium (128). Although widely used, the Marshall CT classification has also been criticised because it uses other information than what is actually seen on the scan, i.e. if a patient was operated or not.

<table>
<thead>
<tr>
<th>CT category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse injury I</td>
<td>No visible intracranial injury on CT scan</td>
</tr>
<tr>
<td>Diffuse injury II</td>
<td>Cisterns present, midline shift 0-5 mm and/or lesion densities present but &lt; 25 cm³</td>
</tr>
<tr>
<td>Diffuse injury III</td>
<td>Cisterns compressed or absent, midline shift 0-5 mm and/or lesion densities present but &lt; 25 cm³</td>
</tr>
<tr>
<td>Diffuse injury IV</td>
<td>Midline shift &gt; 5 mm, lesion densities &lt; 25 cm³</td>
</tr>
<tr>
<td>Evacuated mass lesion</td>
<td>Any lesion surgically evacuated</td>
</tr>
<tr>
<td>Non-evacuated mass lesion</td>
<td>High- or mixed density lesion &gt; 25 cm³, not surgically evacuated</td>
</tr>
</tbody>
</table>

Table 3 Marshall CT classification.

3.3.2.3 Assessment of multitrauma

TBI is often accompanied by extracranial injuries. It is important to note extracranial injuries when studying patient outcome and the secondary insults effect on prognosis, since extracranial injuries may affect outcome and are likely to cause secondary insults. One way to achieve a measure of the total injury burden of the patient is to use the Injury Severity Score (ISS) (15). The ISS is based on a simple injury severity scale called the Abbreviated Injury Scale (AIS) (159). The AIS consists of ratings (1-5) for all types of injuries within six different body regions (head/neck, face, thorax, abdomen/pelvis, extremities and superficial layers). The ISS is obtained by the sum of squares of the most severe injuries from three different body regions and has been shown to be a reliable predictor of outcome (15).

A more complicated measure of the probability of survival, which combines ISS with GCS, age, respiratory rate and systolic blood pressure is called the TRISS (19). In TBI patients this score has been found to identify patients who will die even though they are not considered to have a severe head injury by the GCS (37). In our studies we wished to assess the influence of age and blood pressure by other means, when the TRISS was not an alternative. Yet another measure of injury severity called the new injury severity score (NISS) has been proposed (136). ISS considers at most one injury per body region and ignores the fact that multiple injuries can be confined to the same body region. The NISS is the sum of the squares of the three most severe
injuries, regardless of body region. NISS has been shown to separate survivors from non-survivors better than does ISS (136). Multiple intracranial injuries are common, e.g. different kinds of bleedings and contusions. The use of NISS in TBI patients may be a better tool in predicting outcome. In our studies we wished to obtain a measure of the extracranial injuries; thus, the original ISS was assessed for patients in papers I, II, III and V.

3.4 Secondary insult definitions and collections

The insult definitions in paper II were based on the treatment goals in the secondary insult program and on a previous secondary insult study performed in the clinic (51). When planning papers III and V we aimed to use the same definitions as used in paper II, but some had to be adjusted when the results for paper II were considered. Paper IV includes a comparison with data from Edinburgh; thus, insult definitions followed Edinburgh University Secondary Insult Grades (80). The secondary insult definitions used in the papers are presented in Table 4.

The collection of secondary insults in paper II was done utilising surveillance charts from the NICU onto which the nurses had noted one value per hour and variable: intracranial pressure (ICP), cerebral perfusion pressure (CPP), systolic blood pressure (BPs) and temperature. The PaO₂ was analysed regularly, at least every hour, whenever there was a respiratory problem. Blood glucose levels were recorded on a special chart. In all patients glucose was checked and registered regularly, but it was checked more often in patients with diabetes mellitus and in those with presenting high blood glucose values. One registration of a value exceeding insult limit was counted as one insult.
Table 4 Thresholds and treatment goals for secondary insults.

While papers I and II were in preparation, a computerised multimodality monitoring system was installed and developed at the NICU. This system collects physiological data from bed space monitors and sends one value per minute and channel (secondary insult variable) to a central server where data are saved. All data were validated utilising patient records (174) before analyses were performed. The general policy was to leave data as valid if nothing in the patient record could conclude whether a divergent value was an artefact or not. This was done so that valid secondary insults were not excluded. The data collection was interrupted when the patient was taken to the operating theatre or radiology department. Data could also be lost due to software, network or system failures. Subtracting these missing periods and the data judged to be invalid from the total monitoring time, gave the “good monitoring time” (GMT) (173).

The amount of insult was calculated as the time spent above/below the insult limit for a specific insult divided by the GMT of that insult channel and patient. Accordingly, the insult measure was presented as a percentage.

3.5 Patient follow-up

To describe outcome, the Glasgow outcome scale (GOS) (75) and Glasgow outcome scale extended (GOSE) (76) were used. The GOS is an ordinal...
scale consisting of 5 levels: dead (D), vegetative state (VS), severe disability (SD), moderate disability (MD) and good recovery (GR). The GOSE is an 8 level scale derived from the GOS scale where the 3 highest levels are divided into an upper and a lower category (Table 5). The scales aim at describing disability and handicap rather than impairment (190, 203) and they have been tested for reliability, sensitivity and validity (190, 204).

It has been recommended that patient follow up after TBI should be performed 6 months after trauma (190). In paper I, follow-up was performed ≥ 6 months post trauma because the study was retrospective and work began after the end of the time period studied. In papers III, IV and V the follow-up time was 6 months. In all studies a structured interview questionnaire proposed by Wilson and coll. (203) was used. A questionnaire was sent by mail (202) and was filled in by either the patient or a relative. When there were doubtful answers, the patient was interviewed by phone (141). In paper I, patients were allocated into GOSE categories. In papers III, IV and V, GOS was used because the aim was not to characterise patient outcome, and in the statistical analyses the dichotomised favourable (MD + GR) and unfavourable (D + VS + SD) categories were used.

<table>
<thead>
<tr>
<th>GOS categories</th>
<th>Summary</th>
<th>GOSE categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Vegetative state</td>
<td>VS</td>
<td>VS</td>
</tr>
<tr>
<td>Severe disability</td>
<td>SD</td>
<td>SD-Lower</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD-Upper</td>
</tr>
<tr>
<td>Moderately disabled</td>
<td>MD</td>
<td>MD-Lower</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MD-Upper</td>
</tr>
<tr>
<td>Good recovery</td>
<td>GR</td>
<td>GR-Lower</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GR-Upper</td>
</tr>
</tbody>
</table>

Table 5 Outcome categories of GOS and GOSE. Table modified from Teasdale and coll. (190).

### 3.6 Statistical Methods

In all calculations p < 0.05 was used as the significance level. In papers I, IV and V, a chi-square test was used when comparing differences in proportions between groups. In papers III, IV and V, normally distributed continuous data were analysed with a t-test to compare group means and the Pearson correlation was used when searching for correlations. For non-normally dis-
tributed data, group medians were compared using the Mann-Whitney U test and correlations were analysed with the Spearman rank correlation.

In papers II and III, univariate logistic regression was used to evaluate the admission- and secondary insult variables’ effect on outcome (papers II and III). To explore the independent effect of insult variables on outcome, multiple logistic regression models were made. In paper III, an ROC curve of the final multiple regression model showed the sensitivity and specificity of the model and the predictive value on the individual level.

In papers IV and V, some results were obtained using a Bayesian neural network system developed earlier by one of the collaborators (130). The neural network was used as an extension of the logistic regression enabling non-linear relationships with a binomial outcome to be investigated.
4. RESULTS

4.1 Paper I

The main observation in paper I was that outcome of patients with traumatic brain injury had improved overall after the establishment of a secondary insult program and standardised care, although no other specific intervention (e.g. drug, operation method) had been introduced (Figure 5). Wärme and coll. had earlier shown that patient outcome had improved after the establishment of the NICU (Figure 5) (198). They also showed that patients with GCS M 4-6 benefit more from NIC than more severely injured patients. Therefore, and to avoid possible influence of differences in patient characteristics between the periods, patients with GCS M 4-6 were analysed separately. In this patient group, the improvement of outcome was even clearer with a decrease in mortality from 27% to 2.8 and an increase in favourable outcome from 68% to 84%, when the two last periods were compared. Obviously, the refinement of the care and the emphasis of avoidance, early discovery and effective treatment of secondary insults, enhanced the recovery of the patients further.

Figure 5 Outcome presented as percent of patients in the different GOS categories before establishment of the NICU, after establishment of NICU and after establishment of a secondary insult program and standardised NIC.
Causes of accidents are listed in Table 6. Forty-four percent of the patients had major extracranial injuries requiring hospital admission. All patients had some kind of pathology visible on the first CT scan. According to Marshall’s CT classification (112), 73% had diffuse injury (signs of swelling, no mass lesion > 25 cm$^3$). Of those, 21% eventually needed surgery. Twenty-seven percent of the patients had a mass lesion, most of which were surgically evacuated.

Another interesting finding in Paper I was that a considerable part of the patient series consisted of patients older than 40 years. Patients 40-59 years of age had virtually the same prognosis as patients 16-39 years of age measured in terms of favourable (GR + MD), unfavourable (SD + VS) and dead; both groups had close to 80% favourable outcome, 15% unfavourable and 5% dead. Patients 60-79 years of age had a worse outcome with 65% favourable, 22% unfavourable and 13% dead.

<table>
<thead>
<tr>
<th>Cause of accidents</th>
<th>Percent of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor vehicle occupant</td>
<td>29</td>
</tr>
<tr>
<td>Pedestrian</td>
<td>12</td>
</tr>
<tr>
<td>Cyclist</td>
<td>1.9</td>
</tr>
<tr>
<td>Work</td>
<td>9.7</td>
</tr>
<tr>
<td>Domestic</td>
<td>4.5</td>
</tr>
<tr>
<td>Sport</td>
<td>10</td>
</tr>
<tr>
<td>Assault</td>
<td>3.9</td>
</tr>
<tr>
<td>Fall and alcohol</td>
<td>23</td>
</tr>
<tr>
<td>Other</td>
<td>4.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Table 6 Cause of accidents in 154 patients with TBI.

An investigation of the patients who died after TBI revealed that only two of the 9 patients died as a direct consequence of their head injury. The other 7 patients had clearly aggravating factors such as a malignant tumour or haematological condition, infections or extracranial injuries. Eleven patients who arrived in GCS M 6 (RLS 1-3a) later died or were severely disabled. In this context, those can be considered as “talk and die” and “talk and deteriorate” patients. The two patients who talked and died both were critically ill of other diseases before sustaining head injury. The other nine patients did not actually talk but could obey commands (RLS 3a). Four of them were ≥ 75 years old and one had Alzheimer’s disease. No explanation was found for the remaining four talk and deteriorate patients.
4.2 Paper II

In paper II the occurrence and the prognostic value of secondary insults, counted manually the first week of NIC, were investigated. 1570 insults were identified in 102 (67%) of the 154 patients (range 1-116 insults) (Table 7). One third of the patients (51 patients) did not have any insults, while 22 patients (14 %) had 25 insults or more. In those 22 patients 959 (61%) of all insults occurred. The incidence of specific standard insults is presented in Figure 6.

<table>
<thead>
<tr>
<th>Frequency of insults</th>
<th>Standard insults</th>
<th>Severe insults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Insults</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>51</td>
<td>33.1</td>
</tr>
<tr>
<td>1 - 9</td>
<td>56</td>
<td>36.4</td>
</tr>
<tr>
<td>10 - 24</td>
<td>25</td>
<td>16.2</td>
</tr>
<tr>
<td>≥ 25</td>
<td>22</td>
<td>14.3</td>
</tr>
<tr>
<td>Total</td>
<td>154</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 7 Occurrence of standard and severe insults.

Ninety-six (62 %) of the patients did not have any severe insults (Table 7 and Figure 6). In 58 patients, 320 severe insults were recognised. Fifty-four patients (35 %) had 1-9 severe insults accounting for 102 (32%) of the 320 severe insults. Hence, 218 (68%) of the severe insults were found in 4 patients. The incidence of specific severe insults is shown in Figure 6.
In the univariate logistic regression analysis GCS M on admission, CT class and ISS of the admission variables had a significant effect on outcome. Of the secondary insult variables, blood glucose and the sum of all insults for each patient were significant. In the multiple logistic regression GCS M solely held prognostic information. Thus, none of the secondary insult variables had any independent effect on outcome.
4.3 Paper III

The purpose of paper III was to describe the occurrence of secondary insults collected with a computerised multimodality monitoring system and to evaluate their independent effect on outcome. Eighty-one patients fulfilled the inclusion criteria. The proportions of secondary insults were non-normally distributed among the patients (Figure 7) except for CPP > 70 mm Hg (which was normally distributed, see Figure 8). Most patients spent less-than 5% of GMT at insult level, which is illustrated with the ICP insult occurrence in Figure 7. Occurring insults were mostly close to the insult threshold. This can be exemplified by the distributions of ICP- and CPP measurements, see Figures 9 and 10. CPP insults in the lower range (< 60 mm Hg) were mostly seen in the range 50-60 mm Hg and not lower, but CPP insults in the higher range (> 70 mm Hg) were spread over a wider range (Figure 10).

![Figure 7](image)

**Figure 7** Number of patients with different proportions (percent of GMT) of ICP insult (standard and severe).
According to the univariate regression analyses of admission variables, age, GCS M, pupils and ISS had effect on outcome, but in the multiple regression analysis the pupil reactivity was not significant. The odds to make a favourable outcome decreased by 50% comparing patients < 40 years old with patients 40-59 years old and by another 50% comparing patients 40-59 years old with patients 60 years old or more. Patients with a GCS M score of 5-6 had 3.9 times greater odds to make a favourable outcome than patients with a GCS M score of 1-4 on admission. Patients with ISS 25 or more had 75% less odds to reach favourable outcome than patients with ISS < 25.

**Figure 8** Number of patients with different proportions (percent of GMT) of CPP insult (> 70 mm Hg and > 80 mm Hg).

**Figure 9** Distribution of ICP-measurements (percent of GMT) in all patients. Insults in dark grey (standard insult) and black (severe insult).
The univariate logistic regression analyses for secondary insult variables (see Table 8) gave the following results. The proportion of ICP insult did not have a significant effect on outcome. For systolic BP, the chance of making a favourable outcome increased by approximately 40% per increased quintile of time spent at either BPs < 100 or BPs < 90. Contrastingly, BPs > 160 and BPs > 180 were associated with a 40% increased risk of making an unfavourable outcome per increased quintile. Mean BP < 80 and < 70, both showed an increased chance of 50% for favourable outcome per increased quintile of GMT at those levels. Mean BP > 110 and > 120 increased the risk of an unfavourable outcome by about one third for each quintile at those levels. Greater proportions of CPP < 60 were associated with a better chance (60% per quintile) of a favourable outcome. CPP > 70 and CPP > 80 decreased the chance of a favourable outcome by 30% per quintile.
Secondary insults in NIC of patients with TBI

<table>
<thead>
<tr>
<th>Insult variable</th>
<th>OR</th>
<th>CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP &gt; 25</td>
<td>-</td>
<td>-</td>
<td>Ns</td>
</tr>
<tr>
<td>ICP &gt; 35</td>
<td>-</td>
<td>-</td>
<td>Ns</td>
</tr>
<tr>
<td>BPs &lt; 100</td>
<td>1.42</td>
<td>1.03 - 1.98</td>
<td>*</td>
</tr>
<tr>
<td>BPs &lt; 90</td>
<td>1.44</td>
<td>1.05 - 1.97</td>
<td>*</td>
</tr>
<tr>
<td>BPs &gt; 160</td>
<td>0.60</td>
<td>0.42 - 0.84</td>
<td>**</td>
</tr>
<tr>
<td>BPs &gt; 180</td>
<td>0.59</td>
<td>0.42 - 0.84</td>
<td>**</td>
</tr>
<tr>
<td>BPm &lt; 80</td>
<td>1.45</td>
<td>1.04 - 2.04</td>
<td>*</td>
</tr>
<tr>
<td>BPm &lt; 70</td>
<td>1.47</td>
<td>1.05 - 2.06</td>
<td>*</td>
</tr>
<tr>
<td>BPm &gt; 110</td>
<td>0.69</td>
<td>0.49 - 0.98</td>
<td>*</td>
</tr>
<tr>
<td>BPm &gt; 120</td>
<td>0.64</td>
<td>0.46 - 0.91</td>
<td>*</td>
</tr>
<tr>
<td>CPP &lt; 60</td>
<td>1.55</td>
<td>1.10 - 2.19</td>
<td>*</td>
</tr>
<tr>
<td>CPP &lt; 50</td>
<td>-</td>
<td>-</td>
<td>Ns</td>
</tr>
<tr>
<td>CPP &gt; 70</td>
<td>0.71</td>
<td>0.51 - 0.99</td>
<td>*</td>
</tr>
<tr>
<td>CPP &gt; 80</td>
<td>0.69</td>
<td>0.49 - 0.98</td>
<td>*</td>
</tr>
</tbody>
</table>

Table 8 Secondary insults (mm Hg) effect on favourable outcome in the univariate analyses (paper III). Odds ratio (OR) > 1 increases the odds of a favourable outcome, OR < 1 decreases the odds of a favourable outcome.
* p < 0.05   ** p < 0.01

Two multiple models, one including admission variables (age, GCS M and ISS) and BP variables, and one including admission variables and CPP variables showed that both BPs > 160 mm Hg and CPP < 60 mm Hg held independent prognostic information when the admission variables had been controlled for. Increased proportion of BPs > 160 mm Hg decreased the chance of a favourable outcome (OR 0.66) while increased proportion of CPP < 60 mm Hg increased the chance for favourable outcome (OR 1.59). In the final multiple logistic regression model, admission variables, BPs > 160 mm Hg, CPP < 60 mm Hg and ICP were included. Age, GCS M, ISS and CPP < 60 mm Hg each held independent prognostic information (Table 9). Patients with increased proportions of CPP < 60 mm Hg did better than others. The odds of achieving favourable outcome increased 1.59 times (OR 1.59) per increased quintile of the GMT with CPP < 60 mm Hg.
Table 9 Result of final multiple regression model. Odds ratio (OR) > 1 increases the odds of a favourable outcome, OR < 1 decreases the odds of a favourable outcome. * = p < 0.05

In order to show the prognostic value of CPP < 60 mm Hg on outcome when admission variables were controlled for, an ROC curve of the final multiple regression model was made. An optimal sensitivity of 0.65 and an optimal specificity of 0.91 were found. The corresponding positive predictive value was 0.90. This means that when the effect of admission variables was controlled for, high occurrence of CPP < 60 mm Hg predicted a favourable outcome and that patients with an unfavourable outcome had small proportions of CPP < 60 mm Hg.

4.4 Paper IV

In this paper, the occurrence of ICP- and CPP insults and their influence on outcome were described for two patient groups: one group was treated according to an ICP-oriented management protocol (Uppsala) and the other group was treated according to a CPP-oriented protocol (Edinburgh). The ICP insult occurrence was similar, 6% of GMT versus 7% of GMT respectively. The median proportion of CPP < 60 mm Hg was 6% in the ICP-managed patients and 1% in the CPP managed patients (p < 0.001). In the ICP-managed patients, the occurrence of CPP insult (< 60 mm Hg) increased the probability of a favourable outcome, but in the CPP-managed patients the occurrence of CPP insult decreased the probability of a favourable outcome (Figure 11).
Secondary insults in NIC of patients with TBI

Figure 11 Probability of a favourable outcome in CPP- and ICP-treated patients. The maximum likelihood estimate of the probability (solid line) is plotted together with 90% confidence intervals (dashed lines). The tic marks at the top and bottom of the figure represent the proportion of CPP < 60 mm Hg for a given patient who had a certain outcome (top = favourable, bottom = unfavourable).

Patients were further divided into a “low insult group” (CPP < 60 mm Hg less than 10% of GMT) and a “high insult group” (CPP < 60 mm Hg more than 10% of GMT). Only five of the CPP-managed patients were allocated into the high insult group, and all of them died. Of the ICP-managed patients, 24 were allocated to the high insult group. Those patients had significantly more favourable outcomes (71% versus 42%) compared to ICP-managed patients in the low insult group (p < 0.05).

Figure 12 shows histograms of the CPP values of the high insult groups. The ICP-treated patients had almost all of their CPP insults in the 50-60 mm Hg range, a small proportion in the 40-50 mm Hg range and almost no time was spent with CPP < 40 mm Hg. In the CPP-treated patients the clearly dominating insult range was CPP < 40 mm Hg. Four of the five patients also had a severe refractory ICP (≥ 40 mm Hg 71-100% of GMT).
Kristin Elf

The pressure reactivity (the change in ICP when BP changes) was calculated as the slope of the regression of ICP on BP. The hourly mean values for ICP and BPm were calculated for all data in all patients. A regression line could then be fitted in each patient. Twenty-two percent of the ICP-managed patients and 23% of the CPP-managed patients had a negative slope of the regression line, i.e. those patients were pressure active (increase in blood pressure caused ICP to decrease).

In the ICP-managed patients, the pressure reactivity was positively correlated with GOS ($r = 0.22$) (pressure passive patients do better) but this was only a statistical trend ($p = 0.066$). In the CPP-managed patients the pressure reactivity was negatively correlated ($r = -0.36, p < 0.01$) with GOS (pressure active patients do better). The probability of favourable outcome was plotted as a function of the slope of the ICP/BPm regression line for both management groups. The curves were then superimposed and they crossed over each other at a pressure reactivity slope of 0.13 (Figure 13). Patients whose pres-
Sure reactivity slope was less than 0.13 would fare better of a CPP oriented protocol and patients whose pressure reactivity slope was greater than 0.13 would fare better of an ICP-oriented protocol. Using this criterion, 61 patients received the management fit for their condition and 64 patients did not. There were significantly more favourable outcomes in patients receiving a management fit for their condition (64%) compared to patients who did not receive a management fit for their condition (45%, p < 0.05). If it would be possible to give each patient the correct treatment, the favourable outcome would increase from 52% (Uppsala) or 53% (Edinburgh) to 64%.

![Figure 13](image)

**Figure 13** Probability of favourable outcome plotted as a function of pressure reactivity calculated as the slope of the ICP/BPm regression line. The curves for CPP- and ICP-managed patients are superimposed and cross each other at 0.13.

4.5 Paper V

In paper V, the temperature was examined as a secondary insult. In contrast to paper II, hypothermia was analysed in addition to hyperthermia; therefore, the confounding effect of barbiturate treatment was also taken into account. Instead of counting the insults manually, the computerised monitoring system was used and the relationship of temperature to other insult variables studied in paper III was also analysed.

Of the 53 patients who fulfilled the inclusion criteria, 83% experienced some time with hyperthermia (> 38 °C ) and 55% had some time with hypothermia (< 36 °C). Patients who received barbiturate treatment (n = 10) had signifi-
Krisin Elf

Significantly greater proportions of hypothermia than patients who did not receive barbiturate treatment ($p < 0.001$) (Figure 14). Patients admitted with a GCS M score of 1-4 had greater proportions of temperature > 38 °C than patients with GCS M score of 5-6 (median 22.2% of GMT and 11.8% of GMT respectively, $p < 0.05$), and male patients had greater proportions of temperature > 38 °C than female patients (median 18.8% and 5.3% respectively, $p < 0.05$). When barbiturate treated patients were excluded, temperature > 38 °C was more common in patients 40 years or older (median 22.8% versus 6.1% of GMT, $p < 0.01$), in patients with GCS M score 1-4 (median 28.8% versus 8.6% of GMT, $p < 0.05$) and in male patients (median 21.5% versus 5.3% of GMT, $p < 0.05$).

Figure 14 Boxplot of hypothermia (temperature < 36 °C) and intracranial hypertension (ICP > 25 mm Hg) in patients treated with barbiturate and patients not treated with barbiturate. The boxes include values between the 25th and 75th percentile. The line in the boxes represents the median value and the vertical lines represent the range from the 2.5th to the 97.5th percentile.

The ten patients who received barbiturate treatment had higher mean ICP and a greater proportion of ICP insult than the patients who were not treated with barbiturate ($p < 0.01$) (Figure 14). Barbiturate treated patients also had lower mean CPP and greater proportions of CPP < 60 mm Hg ($p < 0.05$). There was a trend ($p = 0.091$) towards lower mean BPs in barbiturate treated patients, they had significantly greater proportions with BPs < 100 mm Hg compared to patients who did not get barbiturate treatment ($p < 0.05$).

Because patients who needed barbiturate treatment belonged to a more severely injured patient population than those who did not need barbiturate treatment, and because barbiturate treated patients were affected by the given treatment, they were excluded from the following analysis. The remaining 43 patients were further divided into two groups based on proportion of
GMT with a temperature > 38°C. The first group called the “less hyperthermia insult group” consisted of patients with < 20% of GMT with hyperthermia and the second group, called the “more hyperthermia insult group” consisted of patients with ≥ 20% of GMT with hyperthermia. When the occurrence of other insults within those two groups was examined, no difference was found for ICP, but a consistent pattern was found for other physiological variables. In the more hyperthermia insult group, patients had greater proportions of high blood pressure and high CPP, whereas patients in the less hyperthermia insult group had greater proportions of low blood pressure and low CPP.

<table>
<thead>
<tr>
<th>Insult variable</th>
<th>Spearman R</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP &gt; 25</td>
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<td></td>
</tr>
<tr>
<td>ICP &gt; 35</td>
<td>Ns</td>
<td></td>
</tr>
<tr>
<td>BPs &lt; 100</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>BPs &lt; 90</td>
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<td>&lt;0.01</td>
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<td>BPs &lt; 80</td>
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<td>BPs &lt; 70</td>
<td>-0.508</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPP &lt; 60</td>
<td>-0.454</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CPP &lt; 50</td>
<td>-0.375</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BPs &gt; 160</td>
<td>0.640</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BPs &gt; 180</td>
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<td>&lt;0.0001</td>
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<tr>
<td>BPs &gt; 110</td>
<td>0.574</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BPs &gt; 120</td>
<td>0.563</td>
<td>&lt;0.0001</td>
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<td>CPP &gt; 70</td>
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<td>CPP &gt; 80</td>
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<td>HRT &gt; 100</td>
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<tr>
<td>HRT &gt; 120</td>
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<td></td>
</tr>
</tbody>
</table>

**Table 10** Correlation analyses between hyperthermia proportions and proportions of specific insults. A positive R value means that an increase in hyperthermia proportion correlates with an increase in proportion of the investigated insult variable.

Those results were supported by significant correlation analyses between hyperthermia proportions and proportions of BPs, BPm and CPP insults. Hyperthermia correlated positively with high BPs, BPm and CPP and negatively with low BPs, BPm and CPP (Table 10). Individual correlations of hourly mean values were significant and positive for a majority of patients when correlations between temperature and ICP, BPs, BPm CPP and HRT were examined.
Outcome was studied by proportions of favourable versus unfavourable outcome in patient groups based on mean temperature. When barbiturate treated patients were included, patients with a low mean temperature had as poor prognosis as patients with a high mean temperature, 67% and 71% unfavourable outcome, respectively. Patients with a mean temperature in the normal range had 36% unfavourable outcome. When barbiturate treated patients were excluded, patients with a low mean temperature had the same prognosis as patients with mean temperature within the normal range, 40% and 37% of patients with unfavourable outcome, respectively. Patients with a high mean temperature still had a poorer prognosis with 71% unfavourable outcome.
5. Discussion

A major advancement in the management of TBI was made when the concept of avoidable factors and their impact on outcome was elucidated. Substantial knowledge about the pathophysiological injury mechanisms has also been obtained. Unfortunately, major efforts that have been put into the productions of neuroprotective drugs have failed thus far and no other invention has been introduced. Therefore, it seems to be of even greater importance to develop the concept of secondary insults and to refine the neurointensive care to further minimise secondary brain injury. This was the reason for the foundation of the secondary insult program and the standardised regimen protocol that was introduced in the NICU. It was satisfying to see that patient outcome, the absolute endpoint, had improved.

It is hazardous to use historical materials for comparison. The patient series studied in paper I did differ in some ways compared to the earlier patient series. The strongest confounding factors were differences in multitrauma occurrence and GCS M score distribution. The former was more common in the last series and does not explain the better outcome of that period. The difference in GCS M distribution was partly overcome by stratification into patient groups, GCS M 1-3 and GCS M 4-6. Wärme and coll. have shown that patients with moderate injuries (GCS M 4-6) benefit more from NIC than more severely injured patients (198). In this patient group (GCS M 4-6), the improvement of outcome was clear with a decrease in mortality from 27% to 2.8% and an increase in favourable outcome from 68% to 84%. This proves that it is meaningful to further investigate the occurrence and prognostic value of different secondary insult variables in order to further improve NIC and patient outcome.

A finding consistent in papers II, III, IV and V was the non-normal distribution of secondary insults among the TBI patients. A large group of patients had little or no insults while a small group of patients suffered from a lot of insults. In paper II, neither ICP, CPP, BP nor PaO₂ were significant predictors of outcome in any analysis. Blood glucose was significant in the univariate analysis, but not in the multiple analysis. As discussed below, TBI-patients may suffer from a hyperdynamic/hyperadrenergic state (33). It is reasonable to believe that the elevated blood-glucose is also a part of this
syndrome, which seems to be dependent on the GCS (34). Also, the sum of all insults for each patient significantly affected outcome in the univariate analysis, but not in the multivariate analysis. The method used to collect and count the insults in paper II was rough, thus insults may have been missed (40). However, one interpretation could be that the insults that occurred were coupled to the primary brain injury, hence not avoidable. If there would have been an independent effect of the insults, it is inferred that the insults that occurred were not a consequence of the primary brain injury, but a result of suboptimal care. The situation with no independent secondary insults may be a prerequisite to enable any significant effect of neuroprotective drugs. Further, the few patients who did suffer several insults may be those who would benefit from some neuroprotective drug that attenuates the cascade processes e.g. excitotoxicity, ROS, inflammation, BBB disruption and oedema development.

In papers III – V the methodology used to collect and describe the occurrence of secondary insults had improved greatly by utilising the high-resolution data recorded by the computerised multimodality monitoring system. In paper III, most of the secondary insult variables studied were significant predictors of outcome in the univariate analyses (see Table 8 page 45); however, ICP was not significant. There may be several reasons for this. Our treatment protocol was primarily aimed at reducing intracranial hypertension and the general occurrence of ICP insult was low and when ICP insult occurred it was close to the insult limit (see Figure 9 page 43). Further, few patients had significant proportions of ICP insult (see Figure 7 page 42) These explanations seem important to consider when evaluating the impact of secondary insults on outcome.

A result that was consistent in papers III and IV was the positive influence that the occurrence of CPP < 60 mm Hg had on outcome in the Uppsala patient series. The theory behind the management concept proposed in Lund is that low CPP might prevent vasogenic brain oedema formation and a secondary elevation of ICP in patients with impaired BBB (10). A theory of the development of vessel damage leading to impaired autoregulation and BBB damage, may include post injury inflammation and free radical damage. A few hours after trauma polymorphonuclear leukocytes (PMNs) accumulate in rat brain (162) and immunoreactive leukocytes have been associated with blood vessels (25). The PMNs produce ROS and reflect an inflammatory phase in which further ROS are formed. The hydroxyl radical (OH') has been shown to cause destructive lesions of the vascular endothelium, sustained dilatation (91) and disruption of BBB with extravasation into the cortex (176).
The positive effect of CPP slightly under 60 mm Hg found in paper III was independent of ICP and therefore may be a result of mechanisms at the cellular and micro environmental level. This suggestion is supported by a microdialysis study by Nordstöm and coll. who found that the extracellular lactate concentrations were significantly higher in penumbra zones compared to other parts of the brain, when CPP was greater than 70 mm Hg (131). A study on cerebral blood flow showed that regional CBF (rCBF) decreased from a normal level to an ischaemic level in contusional low density areas after norepinephrine induced BP- and CPP-increases (27). This could either be due to vasoconstriction or to increased vasogenic brain oedema in a region of disrupted BBB. According to a clinical study of the effect of CPP elevation on PtI0₂, PtI0₂ does not improve when CPP is increased over 60 mm Hg (195). These results support the theory that CPP close to 60 mm Hg is beneficial for CBF and metabolism in the brain after trauma, especially in more injured areas.

A relationship between hyperthermia and high blood pressure, high CPP and elevated heart rate was found in paper V. Syndromes including those symptoms have been described in the literature earlier (17, 33). Clifton and coll. called it “hyperdynamic state” (33). Hyperthermia and hypertension have been shown to be elevated proportionally to the elevation of plasma norepinephrine, which in turn has been found proportional to the GCS (34). In paper V, hyperthermia seemed to be coupled to a more unfavourable prognosis and in paper III hypertension increased the odds of an unfavourable outcome independent of admission variables. Hyperthermia damages the BBB with cerebral oedema as a consequence (168). Hypertension may enhance this vasogenic oedema in a synergistic way. This resumes the hypothesis that lower blood pressure and CPP may be protective against interstitial oedema and metabolic disturbances of the micro environmental level.

When the temperature was studied in paper V, the barbiturate treated patients were excluded from some analyses. Patients treated with barbiturates were expected to differ in insult occurrence compared to the other patients. There were two main reasons for this. Firstly, the indication for barbiturate treatment was intractably high ICP, thus barbiturate treated patients could be anticipated to suffer more ICP insults and possibly to have a more severe injury. Secondly, barbiturates are known to affect other physiological variables than ICP (160, 192), e.g. temperature, which would be important in this context. For the same reasons, but mainly because of the ICP insults, barbiturate treated patients could also be anticipated to have a poorer outcome. Therefore, barbiturate treated patients were excluded in one of the two outcome analyses. As expected, barbiturate treated patients did have significantly lower temperature, more intracranial hypertension, lower blood pressure, lower CPP and higher heart rate than other patients. When barbiturate
treated patients were included in the outcome analysis, low temperature was associated with a greater proportion of unfavourable outcomes, compared to normal temperature. This effect was attenuated when the barbiturate treated patients were excluded from the analysis. Hence, barbiturate treatment is important to take into account when studying the temperature as a secondary insult and the effect of temperature on outcome.

How the treatment protocol used may affect the occurrence and prognostic value of secondary insults was also shown in paper IV, where patients treated in Edinburgh were compared with patients treated in Uppsala. The occurrence of ICP insults was virtually the same but there was a significant difference in occurrence of CPP insults (median 7% in Uppsala, 1% in Edinburgh). In Edinburgh, where the protocol was aimed at keeping CPP > 70 mm Hg, patients who despite the given treatment experienced significant duration of CPP < 60 mm Hg (n = 5), died. In line with this, Clifton and colleagues stated that “one occurrence of CPP less than 50 mm Hg exerts as profound an impact on patient outcome as does age or admission GCS score and far greater impact than high ICP or low BPm alone” (31). In centres using a CPP-oriented management protocol, low CPP is interpreted as an ominous sign. In our study, the five patients in Edinburgh with CPP < 60 mm Hg for a long period of time also had severe refractory ICP insults or severe multiple injuries, and therefore the independent contribution of CPP insults on outcome in those patients is not clear. In Uppsala where treatment was ICP-targeted, CPP insults were found mainly between 50-60 mm Hg and larger amounts of “CPP < 60 insult” were predictive of favourable outcome. Hence, the treatment protocol used affected not only the occurrence, but also the prognostic value of certain insults. This result may explain why polarised opinions regarding appropriate CPP thresholds exist.

The most interesting result in paper IV was that some patients may benefit from an ICP-oriented protocol and some from a CPP-oriented protocol. A breakpoint for the treatment protocol switch was identified using the pressure reactivity, i.e. patients with pressure reactivity < 0.13 seem to benefit from a CPP-oriented management and patients with pressure reactivity > 0.13 seem to benefit from an ICP-oriented protocol. Generally, it can be said that pressure passive patients would benefit from an ICP-oriented management and pressure active patients would benefit from a CPP-oriented management. In paper IV, it was concluded that an overall better outcome would be achieved if it would be possible to adapt treatment individually. Our way of calculating pressure reactivity requires at least 24 hours of monitoring, which is not optimal. Other bed-side methods for assessment of the autoregulatory status have been developed, e.g. transcranial doppler measurement of the middle cerebral artery blood velocity while manipulating blood pressure with thigh cuffs (1) or carotid artery compression (60), as well as

Kristin Elf
analyses of spontaneous fluctuations in the BP (138). Even so, there is currently no established continuous method available to determine whether a patient treated in the NICU is pressure passive or active, or if pressure autoregulation is intact or not.

Czosnyka and coll. have developed a method to measure the moving correlation of ICP and BP based on 40 5-second intervals, the pressure reactivity index (PRx) (44). PRx ≤ 0 indicates preserved pressure reactivity and PRx > 0 a pressure passive reaction. PRx is an independent predictor of outcome; an average PRx > 0.2 has been associated with unfavourable outcome in 81% of the patients, while all patients with mean PRx < -0.2 had a favourable outcome when treated according to a CPP-oriented protocol. An attempt to use the PRx in clinical care has been proposed by Steiner and coll. They identified an “optimal CPP” (CPPopt) where the PRx had its minimum. A correlation was found between the difference of mean CPP and CPPopt and outcome. Patients with mean CPP close to CPPopt did better (183). The CPPopt is an attempt to make the NIC individual. However, it takes about 24 hours to calculate the CPPopt and in the study by Steiner and coll., the CPPopt could only be identified in 60% of the patients (183). Further development of a reliable way to continuously assess the pressure reactivity would be desirable. Thereafter prospective randomised trials could be designed to evaluate the hypothesis that individually selected treatment protocols based on the pressure reactivity (status of the autoregulation) will improve patient outcome.
6. CONCLUSIONS

In this thesis, it has been shown that the outcome of patients with TBI has improved after the establishment of a secondary insult program aimed at avoiding secondary insults during neurointensive care and the introduction of standardised care. The secondary insults that occurred were not equally distributed among the patients. Most patients had almost no insults while a few patients suffered from several insults. This pattern was consistent regardless of collection method.

In the first patient series where insults were manually recorded from surveillance charts, they were not found to contribute any independent prognostic information, interpreted as that the insults that occurred were coupled to the primary brain injury and hence not avoidable. When the computerised minute-by-minute collection system was used in the second patient series, CPP slightly less than 60 mm Hg was found to be predictive of favourable outcome and hypertension was an independent predictor of unfavourable outcome. Hypertension correlated with hyperthermia and these may be a part of a hyperdynamic state possibly aggravating vasogenic brain oedema.

It was found important to consider the effects of barbiturate treatment on secondary insults and outcome. Hypothermia and intracranial hypertension were more common in patients given barbiturate treatment. When barbiturate treated patients were included, outcome was as poor in hypothermic patients as in hyperthermic patients while normothermic patients had better outcome. When barbiturate treated patients were excluded, patients with hypothermia had the same outcome as patients with normothermia, while hyperthermic patients had a worse outcome.

The occurrence and prognostic value of the secondary insults were affected by the kind of management protocol used in the NIC unit. In patients treated according to an ICP-oriented protocol, CPP slightly less than 60 mm Hg was more common and predicted favourable outcome. In patients treated according to a CPP-oriented protocol, CPP insults were rare and predictive of unfavourable outcome. If patient treatment could be individualised and guided by the presence or absence of pressure reactivity, the patient outcome could improve even more.

Det primära omhändertagandet av patienter med THS på olyckplatsen har sedan dess förbättrats och prognosen blivit bättre. Stora forskarinsatser om de cellulära skademekanismerna har vidare bidragit till ökad kunskap. Stort hopp har ställts till utvecklingen av så kallade neuroprotektiva läkemedel. I kliniska studier har dock inget läkemedel visat positiv effekt på patienter och därför finns ännu inget läkemedel tillgängligt. Förbättrad neurointensivvård med färre sekundära insulter och mindre sekundär hjärnskada skulle kunna förbättra behandlingsresultaten ytterligare.

I Uppsala infördes på 1990-talet ett program mot sekundära insulter och ett standardiserat vårdprotokoll, med syfte att minimera förekomsten och effektivisera behandlingen av sekundära insulter. Målen med denna avhandling var att utvärdera behandlingsresultaten hos patienter med THS efter dessa åtgärder och att beskriva förekomsten och den prognostiska betydelsen av sekundära insulter samt att undersöka hur olika vårdprotokoll påverkar förekomst och prognostisk betydelse av sekundära insulter.

Av de 154 vuxna patienter som vårdades pga THS på neurointensivvårdsavdelningen (NIVA) under 1996-97 hade 79% återgått till ett oberoende liv och 6% hade dött 6 månader efter trauma. Detta kan jämföras med en grupp patienter som vårdades under 1987-88, av vilka 48% återgick till ett självständigt liv och 31% dog. Även om jämförelser med historiska material ska göras med försviktighet tycks det som att prognosen för THS-patienter hade
förbättrats efter att standardiserad vård införts och programmet mot sekundära insulter genomförts.


För att kunna spara och bearbeta data med större precision (ett mätvärde per minut och fysiologisk variabel) installerades och utvecklades en särskild programvara, the Browser, och en databas byggdes upp. En ny patientserie analyserades och denna gång var både blodtryck (högt och lågt) och cerebralt perfusionstryck (CPP) (högt och lågt) men ej intrakraniellt tryck (ICP) signifikanter i den univariata analyser. I en multipel logistisk regressionsmodell gav större andel monitorerad tid med blodtryck > 160 mm Hg sämre odds för ett oberoende liv (OR = 0.66). Likaså gav större andel monitorerad tid med CPP < 60 mm Hg prognostisk information oberoende av andra variabler, men med ett ökat odds för ett oberoende liv (OR = 1.59).

I Uppsala var vårdprotokollet primärt inriktat mot kontroll av det intrakraniella trycket (< 20 mm Hg). Andra kliniker, framförallt utomlands, använder behandlingsprotokoll som primärt är inriktade på att upprätthålla det cerebrala perfusionstrycket (> 70 mm Hg). För att kunna utvärdera behandlingsprotokolls betydelse för förekomst och prognostisk betydelse av sekundära insulter studerade vi patienter vårdade i Uppsala och i Edinburgh. Patienter vårdade med ett CPP-orienterat protokoll (Edinburgh), hade signifikant mindre andel monitorerad tid med CPP < 60 mm Hg. Förekomst av CPP < 60 mm Hg var hos dem kopplat till en dålig prognos medan förekomsten av CPP < 60 mm Hg hos patienter behandlade enligt det ICP-baserade protokoll (Uppsala), var kopplat till en god prognos.

Vi studerade också hur tryckreaktivitet (relationen mellan blodtryck och intrakraniellt tryck), mätt som lutningen av regressionslinjen för intrakraniellt tryck som funktion av blodtrycket, påverkade behandlingsresultatet. I både Uppsala och Edinburgh var ca 20% av patienterna tryckaktiva (intrakraniella trycket sjunker då blodtrycket stiger). I Uppsala var en tryckpassiv reaktion (intrakraniella trycket följer blodtrycket) kopplat till en god prognos medan en tryckaktiv reaktion var kopplad till en god prognos i Edinburgh. Sannolikheten för att återgå till ett självständigt liv beräknades som en funk-
tion av tryckreaktiviteten. Patienter med en tryckreaktivitet < 0.13 hade större sannolikhet att återgå till ett självständigt liv med det CPP-baserade protokollet medan patienter med tryckreaktivitet ≥ 0.13 hade större sannolikhet att återgå till ett självständigt liv med det ICP-baserade protokollet. Om patienterna kunde behandlas efter det protokoll som bäst passar till deras tryckreaktivitet skulle andelen patienter med bra behandlingsresultat öka med ca 10 procentenheter i både Uppsala och Edinburgh.

Slutligen studerade vi temperatur som en sekundär insult, dess koppling till de andra fysiologiska variablerna samt till prognosen. Även här behövdes hänsyn tas till den givna behandlingen då svårt skadade patienter med högt intrakraniellt tryck behandlades med barbiturat som också sänker temperaturerna. Generellt var hypertermi korrelerat till hypertoni och takycardi (snabb puls). Detta kan vara symptom på ett hyperdynamiskt tillstånd som kan misstänkas öka risken för hjärnsvullnad. De barbituratbehandlade patienterna hade signifikant mer högt intrakraniellt tryck och mer hypotermi än de andra patienterna. Då dessa inkluderades i prognosanalysen var både hypotermi och hypertermi kopplat till dålig prognos med endast ca 30 % som återgick till ett självständigt liv. Om de barbituratbehandlade patienterna exkluderades hade patienter med hypotermi lika bra prognos som patienter med normal kroppstemperatur med ca 60% självständigt liv.
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Secondary insults in NIC of patients with TBI

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Secondary insults in NIC of patients with TBI

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