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Intracranial Compliance and Secondary Brain Damage. Experimental and Clinical Studies in Traumatic Head Injury.

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Abstract

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Traumatic brain injury (TBI) renders the brain more vulnerable to secondary insults. The increased vulnerability can probably be explained by a combination of disturbances in hemodynamics, metabolism and craniospinal dynamics. Reduced ability to compensate for added intracranial volume, i.e. reduced intracranial compliance (IC), is one possible mechanism. The *aim* of this thesis was to study the role of IC on the effect of secondary insults after TBI.

A rat TBI model was developed where IC could be altered without causing pathological increases in intracranial pressure (ICP). Reduction of IC was made by placing rubber film between the dura mater and bilateral bone flaps. A reduction of IC in terms of reduced Pressure Volume Index was confirmed. Microdialysis (MD) of extracellular fluid was used to monitor neurochemical changes. Reduced IC after TBI proved to increase the vulnerability of the brain to secondary intracranial volume insults according to neurochemical microdialysis markers. Reduced IC or intracranial volume insults alone did not cause any metabolic changes as compared to controls. Moderate posttraumatic hypotension (50mmHg for 30 min) induced 2 hrs after TBI, did not aggravate posttraumatic extracellular neurochemical changes significantly, irrespective of the level of IC. Although controversial, a mild to moderate hypotensive insult after initial posttraumatic stabilization may not be as detrimental as earlier believed.

The Spiegelberg Compliance Monitor and MD were simultaneously used in 10 TBI patients to get an impression of the clinical value of IC monitoring and the relationship between IC, temperature and MD Lactate/Pyruvate ratio. IC and MD could be monitored simultaneously in TBI patients. Higher L/P ratios were seen when IC was low. Patients with induced coma treatment had significantly higher average L/P ratios, possibly due to their poorer neurological condition. An indication was also found that in TBI patients with high temperatures, L/P ratio rose as IC decreased, but in patients with low temperature there was no effect of IC on L/P ratio. These data suggest the importance of avoiding hyperthermia in TBI patients, especially in patients with low or decreased IC (monitored or anticipated).

Keywords: Traumatic brain injury, Intracranial compliance, Secondary insults, Microdialysis, Neurointensive care

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Kunskapens rötter är
bittra, men dess fruk-
ter söta.

Aristoteles

This book is dedicated to my family and friends

PAPERS

This thesis is based on the following papers, which will be referred to by their roman numerals.

- I Salci K, Enblad P, Piper I, Contant C and Nilsson P.
A model for studies of intracranial volume pressure dynamics in traumatic brain injury.
J Neurotrauma (2004), 21, 317-327.
- II Salci K, Nilsson P, Goiny M, Contant C, Piper I and Enblad P.
Low intracranial compliance increases the impact of intracranial volume insults to the traumatised brain. A microdialysis study in a traumatic brain injury rodent model.
Neurosurgery (2006), 59, 367-73.
- III Salci K, Enblad P, Goiny M, Contant C, Piper I and Nilsson P.
Neurochemical impact of hypotensive insults after traumatic brain injury at different levels of intracranial compliance studied in a brain trauma rat model.
Submitted
- IV Salci K, Nilsson P, Howels T, Ronne-Engström E, Piper I, Contant C and Enblad P.
Intracerebral microdialysis and intracranial compliance monitoring of patients with traumatic brain injury.
J Clin Monit Comput. (2006), 20, 25-31.

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ABBREVIATIONS

ATP	Adenosine triphosphate
AMP	Adenosine monophosphate
BP	Blood pressure
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CPP	Cerebral perfusion pressure
CSF	Cerebrospinal fluid
CT	Computerized tomography
DI	Diffuse injury
ECF	Extracellular fluid
EDH	Epidural hematoma
FPI	Fluid percussion injury
GCS	Glasgow coma scale
GOSE	Glasgow outcome scale, extended
IC	Intracranial compliance
ICH	Intracerebral hematoma
ICP	Intracranial pressure
ISS	Injury severity score
L/P ratio	Lactate/pyruvate ratio
MABP	Mean arterial blood pressure
MD	Microdialysis
NIC/U	Neurointensive care / unit
PVI	Pressure volume index
Ro	CSF outflow resistance
SAH	Subarachnoid hemorrhage
SEM	Standard error of the mean
SD	Standard deviation
TBI	Traumatic brain injury
VPR	Volume pressure response

INTRODUCTION

Traumatic brain injury (TBI) is a major health problem globally, afflicting a relative large number of people and being a major cause of death and disability (Pickard 1993, Narayan 2002). Several reports have indicated a TBI incidence of about 200 cases per 100 000 in the Western world and approximately 10-15 % are regarded as severe injury (Socialstyrelsen 1988, Romner 2000, Bruns 2003). The sequelae after TBI, in terms of disability and cognitive dysfunction, have a profound impact on the life of these survivors and their families but also on society as a whole, since the incidence of TBI peaks in adolescents and young adults (Ponten 1995, Bruns 2003, Olesen 2003). The outcome for these patients has improved during the last decades both in terms of mortality and morbidity. This has mainly been a result of better understanding of the pathophysiology of the brain injury, better diagnostic tools, better monitoring techniques and also by the creation of special neurologic intensive care units (NICU) for this patient category (Becker 1977, Bowers 1980, Miller 1981, Warne 1991, Elf 2002). All of the improvement can be related to early detection and thereby reduction of the secondary insults that might aggravate the primary brain injury in these patients (Reilly 1975, Becker 1977, Rose 1977, Miller 1978, Marshall 1979, Bowers 1980, Miller 1982, Marshall 1983, Nordstrom 1989, Sharples 1990, Warne 1991, Piek 1992, Elf 2003).

Despite several promising experimental drug trials, no clinical drug trial has so far shown any beneficiary effect on outcome in TBI patients. One reason for this is probably the complexity and heterogeneity of TBI in patients (Narayan 2002). In order to further improve and develop care of these patients it is important to increase the understanding of the complex mechanisms behind secondary injury after TBI. The occurrence of different physiological disturbances (i.e. secondary insults) and their impact on the injured brain still remain a challenge in TBI research.

BACKGROUND

PRIMARY BRAIN INJURY

Any trauma resulting in external forces applied to the head, either direct contact or relative motions (acceleration/deceleration), might cause brain injury by destruction, displacement or heavy tissue strains (Goldsmith 1966, Stalhammar 1986, Gennarelli 1994, McLean 1997). This mechanical tissue injury also called the primary injury, can be open/penetrating injury or closed head injury. In humans, the majority of TBI is closed head injuries (Gutierrez 2001) and is most commonly classified as either focal brain injury (contusions, hematomas) or diffuse brain injury, i.e. diffuse axonal injury (McIntosh 1996). The degree of primary brain injury depends on the type of external force and its effect on the skull and brain and is reflected by the degree of consciousness of the patient.

SECONDARY BRAIN INJURY

Secondary brain injury cellular events

TBI causes a multitude of disturbances on the cellular level apart from the initial mechanical damage. These include cellular depolarization, cell membrane dysfunction with disturbance of ion homeostasis, excessive release of excitatory amino acids (EAA), free radical production, mitochondrial damage, vascular damage, disruption of the blood-brain-barrier (BBB), inflammation, impaired cerebrovascular autoregulation and edema formation (Faden 1989, Katayama 1990, Nilsson 1990, Faden 1992, Nilsson 1993, Siesjo 1993, Povlishock 1995, Conti 1998, McIntosh 1998, Zipfel 2000). A cascade of secondary events may cause a secondary brain injury in addition to the initial

damage. Whether this cascade of cellular events after TBI can be altered by pharmacological means has been the focus of several experimental and clinical drug trials on TBI (Doppenberg 1997, Narayan 2002).

Excessive release of the EAA glutamate is believed to cause excitotoxicity by over-stimulation of glutamate receptors, such as the NMDA-receptors, and results in calcium (Ca^{2+}) and sodium influx. This causes a passive influx of chloride and water resulting in cellular oedema (Zipfel 2000). Treatment with NMDA receptor antagonist has shown some beneficiary effects in experimental studies of ischemia with a reduced ischemic lesion (Ozyurt 1988, Park 1988, Gotti 1990, Gill 1992, Valtysson 1994). The most important ionic disturbance after TBI is believed to be the intracellular influx of Ca^{2+} causing secondary damage through mitochondrial damage, increase in free radical production, activation of enzyme systems with destructive properties and gene expression changes (McIntosh 1998). Experimental TBI studies have shown that treatment with nitrones improves functional and morphological outcome in rats, an effect believed to be mediated by reduction of the free radical formation after TBI (Sen 1994, Marklund 2001a, Marklund 2001b). While various experimental drug studies (glutamate-, calcium-, and bradykinin antagonists, respectively, free radical scavengers, steroids and anti-convulsants) have shown somewhat encouraging results after experimental TBI, all studies reaching clinical trials have failed to show any improvement in outcome of TBI patients (Narayan 2002). These posttraumatic disturbances contribute to the vulnerability of the brain for both systemic insults (e.g. hypotension, hypoxia, hyperthermia) and intracranial insults (e.g. hemorrhages, edema, seizures), see below.

Secondary insults and avoidable factors

In the 1970's it was observed that patients who had talked after a head injury later deteriorated and died (Reilly 1975, Rose 1977). Autopsies revealed the development of intracranial hematomas or cerebral contusions with fatal brain swelling. It was also noted that some had hypoxic/ischemic brain damage without intracranial hematomas, probably related to poorly controlled epilepsy, meningitis, hypoxia or hypotension. The fact that these patients were conscious and able to talk after their head injury indicated that the primary injury was mild. The fatal outcome in these patients was explained by an increased vulnerability of the injured brain to secondary insults. Since the secondary insults mainly appeared to have been avoidable, the term "avoid-

able factors” was introduced (Rose 1977). The insights concerning “avoidable factors” and “talk and die” patients, laid the foundation for modern management of TBI patients, where focus was placed on observation of the neurological state and monitoring of physiological parameters in order to detect and treat secondary insults early. The ultimate goal being to avoid or reduce the secondary brain injury seen in these patients.

Even with advanced monitoring techniques and modern medical care, secondary insults still occur, during all stages of care (Sharpley 1990, Chesnut 1993a, Jones 1994, Winchell 1996, Signorini 1999, Elf 2002, Elf 2003).

Increased intracranial pressure (ICP), defined as a pressure more than 20 mmHg, occurs commonly in patients with severe head injury and is associated with a poorer outcome (Becker 1977, Miller 1977, Marshall 1979, Pitts 1980, Miller 1981). Fever is common in NIC patients (Kilpatrick 2000), has a direct effect on ICP (Rossi 2001) and is known to worsen neurological outcome (Dietrich 1992, Kilpatrick 2000). Systemic hypotension has been shown to occur frequently (15-35 % of patients) in severe head injured patients and was associated with a significant increase in mortality and morbidity (Miller 1978, Miller 1981, Miller 1982, Miller 1985, Luerssen 1988, Chesnut 1993a, Chesnut 1993b, Manley 2001). It seems like both early posttraumatic systemic hypotension (occurring from the time of injury through resuscitation) as well as late posttraumatic systemic hypotension (in the NIC) have a significant impact on mortality and morbidity in TBI patients (Chesnut 1993a, Manley 2001). In a study by Winchell and colleagues it was noted that transient hypotension (systolic BP < 100 mmHg) was common during NIC of severe TBI patients (55% of the patients suffered from at least one event) and was associated with poorer outcome (Winchell 1996). It has also been shown that moderate and severe episodes of hypotension were more strongly associated with outcome (Barton 2005).

Experimental studies have also shown synergistic effects of TBI and secondary systemic hypotension resulting in increased contusion volume (Matsushita 2001), increased reduction of high-energy phosphates (ATP) (Ishige 1988), and reduction of cerebral blood flow (CBF), cerebral oxygen delivery and EEG activity, respectively (DeWitt 1992, Schmoker 1992).

Microdialysis monitoring of secondary brain injury

In the 1970's microdialysis (MD) technique was introduced (Delgado 1972, Ungerstedt 1974). The MD system consists of a small double lumen probe with a semi-permeable membrane at the tip. The probe is implanted in the tissue and perfused at a constant rate, with a fluid isotonic to the extracellular fluid (ECF). Diffusion allows for transport of different agents across the membrane. In brain research this new method was important since it enabled studies of brain neurochemistry in the interstitial space without the need for tissue extraction. The neurochemical changes related to brain injury could be studied in detail and the understanding of the injury mechanisms could be increased. The first human brain MD studies were done in the frontal lobe during tumor removal (Hillered 1990) and in the thalamus of Parkinson patients (Meyerson 1990). For more technical MD details see the materials and methods section ahead.

The brain has a high energy consumption in order to maintain its electrical activity and function, and hence high energy demands. The brain is dependent on glucose as an energy-source and oxygen for its metabolism. Any interference with this constant supply of glucose and/or oxygen may result in dysfunction and subsequent injuries to the brain. The energy and oxygen supply to the brain is maintained through the cerebral blood flow (CBF). Glucose in the cells is first metabolized to pyruvate yielding ATP and NADH. The main ATP production in the cell take place in the mitochondrial respiratory chain where pyruvate, during aerobic conditions is further metabolized and ATP produced. During ischemia, lack of oxygen at the mitochondrial level leads to an altered redox state with accumulation of NADH, and this shifts the lactate dehydrogenase reaction toward lactate resulting in an increased lactate and lactate/pyruvate ratio (Siesjo 1984). When the cells are subjected to ischemia high energy phosphates, such as ATP and phosphocreatine, decrease (Marshall 1975) and this result in the formation of the AMP break down products adenosine, inosine, hypoxanthine and xanthine (Siesjo 1984). Interstitial levels of glucose, lactate and pyruvate provide information on glucose delivery and utilization, the extent of anaerobic glycolysis and also information of the intracellular redox state since this is reflected by the interstitial lactate/pyruvate ratio (Siesjo 1984, Persson 1992, Hillered 2005). Interstitial hypoxanthine ads further information about the ongoing energy failure.

Experimental MD studies have shown that TBI is followed by transient increases of interstitial lactate, LP-ratio and hypoxanthine in the trauma region and is believed to represent a transient metabolic disturbance related to the trauma (Nilsson 1990, Bell 1998). In TBI patients it has been shown that MD

markers for glucose metabolism may be of value for detecting hypoxia/ischemia (Landolt 1994, Langemann 1995, Hutchinson 2000, Vespa 2003). During cerebral ischemia/hypoxia there is a marked increase of dialysate lactate, LP-ratio and a marked decrease of glucose (Langemann 1995, Enblad 1996, Persson 1996, Robertson 1998, Valadka 1998, Goodman 1999, Hutchinson 1999a, Hutchinson 1999b, Unterberg 2001). MD-hypoxanthine has also been shown to be increased during such conditions (Persson 1992, Enblad 1996, Persson 1996, Bell 2001). The reliability of these MD markers to represent hypoxia/ischemia has been shown in relation to other methods for detecting this condition. Severe ischemia, based on PET (positron emission tomography) criteria, resulted in an increase in MD-L/P ratio (Enblad 1996). Episodes with S_{jv}O₂ (jugular venous oxygen saturation) below 50% or ICP > 25 mmHg were associated with increased MD-lactate (Robertson 1995, Goodman 1996b). A drop in P_{ti}O₂ (brain tissue PO₂) resulted in increased MD-lactate and L/P ratio (Robertson 1998, Valadka 1998) and CPP below 50 mmHg was associated with increased MD-lactate and MD-L/P ratio in samples from areas of tissue at risk (Nordstrom 2003).

Several other MD markers on the state of the brain tissue also exist (Hillered 2005). Experimental studies have shown that cerebral ischemia and epilepsy caused a membrane phospholipid (PL) degradation and creation of free fatty acids (Bazan 1970). The mechanism behind this is believed to be that factors associated with cerebral ischemia/hypoxia (energy failure, Ca²⁺ influx etc) leads to phospholipase activation resulting in membrane PL degradation into free fatty acids and glycerol. This process can cause cell membrane dysfunction, cellular edema and ultimately cell death (Chan 1982, Farooqui 1994). The water soluble glycerol could easily be measured and thus serve as a marker of PL degradation in cerebral ischemia and epilepsy (Gercken 1973, Paschen 1986). In experimental studies it has been shown that MD-glycerol is increased after TBI (Marklund 1997) and cerebral ischemia (Frykholm 2001). MD-glycerol has also been shown to be increased in clinical studies of TBI and focal ischemia (Hillered 1998, Grande 2000, Reinstrup 2000).

INTRACRANIAL DYNAMICS

The history of intracranial dynamics started with the Monro-Kellie doctrine (Monro 1783, Kellie 1824) which proposed that the brain and its contained blood were incompressible, enclosed in a rigid skull, of which the total volume remained constant. In its original form it did not take into account CSF as a component. Burrows introduced the concept of reciprocal volume

changes between blood and CSF (Burrows 1846) and this concept was later extended to allow for reciprocal changes in all the craniospinal constituents. Kocher described in 1901 the stages of cerebral compression related to the expansion of intracranial brain tumors, i.e. volume compensation by CSF and venous blood (Kocher 1901). Ayala, studying the fall in lumbar pressure when CSF was removed from patients, was the first to describe the “elasticity of the meninges” (Ayala 1925). However, there was also reports that lumbar CSF pressure in some patients was at times normal despite the fact that the patients showed clinical signs of brain compression (Smyth 1938, Evans 1951). Though it had been known earlier, Langfitt and colleagues described this phenomenon of *pressure underestimation* where, during later stages of progressive supratentorial brain compression, a loss of ICP transmission across the tentorial hiatus occurs and ICP recordings infratentorially (including lumbar CSF space) underestimate the supratentorial pressure (Langfitt 1964a, Langfitt 1964b). Guillaume and Janny were the first to introduce continuous intraventricular ICP monitoring into clinical neurosurgical practice in 1951 (Guillaume 1951). The modern era of ICP monitoring started with the work of Nils Lundberg who measured intraventricular pressure in patients and was the first to describe the frequency with which raised ICP occurs clinically and also described different spontaneous pressure wave fluctuations (Lundberg 1960).

Increased ICP in man, (> 20 mmHg), appears commonly in patients with severe head injury and has been found to be associated with worse outcome (Becker 1977, Miller 1977, Marshall 1979, Pitts 1980, Miller 1981). The craniospinal axis can be regarded as a closed system. This means that the elastic, or its inverse, the compliant, properties of this system will determine what additional volume can be added before ICP begins to rise. The volume/pressure ratio ($\Delta V/\Delta P$) or compliance of the system is equal to the slope of the volume versus the pressure curve and can be obtained by injecting known amounts of fluid into the cerebrospinal fluid (CSF) space and recording the rise in CSF pressure (or withdrawal of volume and record the decrease of pressure) (figure 1). Löfgren and later Marmarou have experimentally shown that the spinal compartment accounts for approximately 30 % of the total compliance of the craniospinal system (Löfgren J 1973, Marmarou 1975).

Changes in ICP affect the cerebral blood flow (CBF) through changes in cerebral perfusion pressure (CPP). Mean CPP = MABP – mean ICP, where MABP stands for the mean arterial blood pressure.

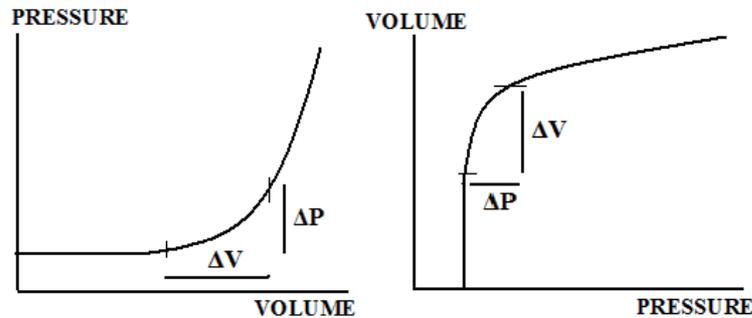


Figure 1. Intracranial pressure-volume relationship or elastance (left) and volume-pressure relationship or compliance (right).

Ryder and colleagues were the first to describe the craniospinal volume-pressure relationship as a non-linear “hyperbolic” function, meaning that for equal volume injections the ratio $\Delta V/\Delta P$ (compliance) decreases as pressure increases (Ryder 1951) (figure 1).

Marmarou developed this concept further, when he mathematically described the craniospinal volume-pressure relationship and demonstrated that the non-linear craniospinal volume-pressure relationship could be described as a linear relationship relating the logarithm of pressure to volume. The slope of this relationship was termed the pressure-volume index (PVI), and in equation form:

$$PVI = \Delta V / \log_{10} (P_m/P_0)$$

P_0 is the baseline pressure and P_m the maximal pressure after injection (see figure 4, page 23). The PVI value stands for the volume required to increase ICP tenfold as compared to the pressure at which it is evaluated (Marmarou 1975). Unlike IC, PVI characterizes the craniospinal volume-pressure relationship over the whole physiological range of ICP. Marmarou also found that the IC was inversely related to the ICP at which it is evaluated, and that the degree to which it is inversely related is proportional to the PVI, which in equation form is:

$$IC = 0.4343 * PVI / ICP$$

Since there is a direct proportionality between IC and PVI at a given ICP, Marmarou concluded that the terms PVI and IC are interchangeable

(Marmarou 1975). Marmarou also concluded that, since it has been shown that the compliance of the CSF system under normal conditions maintains a fixed exponential relationship to pressure for extended periods, the pressure-volume curve may be regarded as a fundamental property of the system. This principle makes it possible to calculate IC from a single volume injection, since the PVI represents a straight line. Once PVI is calculated, IC can be calculated at any given registered pressure using the formula above.

The balance between CSF production and absorption also affects the cranio-spinal volume-pressure relationship and the absorption can be affected by intracranial pathology with increased CSF outflow resistance. Marmarou's mathematical model improved understanding of the static and dynamic processes of formation and absorption of CSF and his mathematical model also included a formula for calculation of CSF outflow resistance from a bolus injection method (Marmarou 1975) (for formula see material and methods section ahead).

PVI has been used as a measure of IC both clinically and experimentally (Sullivan 1977, Shapiro 1982, Kosteljanetz 1986, Maset 1987). In a pediatric study it was found that when PVI was reduced by 80% of predicted control value it was an accurate indicator of impending intracranial hypertension (Shapiro 1982). Tans and Poortvliet reported in a patient study that PVI values between 13 and 18 mL, although pathological, usually had no therapeutic consequences. PVI values below 10 mL almost always required reduction of ICP. For PVI values between 10-13 mL their recommendation was either reduction of ICP or close monitoring (Tans 1983). They also reported that determination of PVI seems useful only when baseline ICP is under 20 mmHg, A-waves are absent and B-waves not numerous.

Miller and colleagues showed that the shape of the volume-pressure relationship changes under a variety of conditions between patients and within patients (a shift of the pressure-volume curve) at different times and different circumstances (Miller 1974, Miller 1975a, Miller 1975b). Miller also pointed out that if there was only a single volume-pressure curve then measuring compliance would add no information and ICP alone would suffice in determining the patient's intracranial compensatory state. This highlights the fact that repeated volume-pressure response (VPR) calculations would be necessary. In clinical practice, however there were disadvantages with the injection technique for IC/PVI calculations. These included increased infection risk, variability due to injection speed (and need for repeated measurements) and also a risk of provoking an insult to the traumatized brain with the injection itself. This could put the patient with low IC at risk of developing secondary brain injuries. Another important disadvantage was that these methods did not provide monitoring of IC. For these reasons the IC/PVI tests are not rou-

tinely used in neurosurgical practice, even though it was clear that knowledge of the patients IC was an adjunct to ICP measurements for predicting risk of raised ICP. One method of obtaining data about IC in a less invasive way was to study the ICP waveform pulse amplitude (Avezaat 1986, Czosnyka 1988, Balestreri 2004, Czosnyka 2004). The concept behind this was that with each heartbeat there is a pulsatile increase in cerebral blood volume and the ICP pulse is the intracranial pressure response to this volume increase, and should therefore be related to IC. The ICP wave pulse should therefore increase as IC decreased, provided that the pulsatile volume increase remained constant. The ICP pulse increases in relation to increased ICP (and so indirectly to IC), but since this relationship is dependent on the assumption that the pulsatile blood volume is constant, and this assumption is tenuous in severely injured patients who may have fluctuating cardiovascular function, this technique as a lumped measure of IC has limitations. In clinical practice, however, the ICP waveform pulse, is used by most clinicians as an “estimation” of the intracranial pressure-volume state. For review see (Piper 1997).

The need for a less invasive method that also would allow for monitoring IC in patients seems to have found a technical solution with the development of the Spiegelberg Compliance Monitor (Spiegelberg 1996) (for technical details see materials and methods section). This new technique for IC monitoring in clinical practice is under evaluation in multi-center studies for different diagnoses, including traumatic brain injury (Piper 1999, Piper 2000, Yau 2000, Yau 2002a, Yau 2002b). Knowledge of the patients IC may be important in predicting the risk of developing increased ICP. Reduced compliance is also one possible mechanism behind the increased vulnerability of the brain, since reduced IC under certain circumstances may lead to hemodynamic effects followed by metabolic disturbances and ischemia (Miller 1974, Miller 1975a, Sullivan 1978, Shapiro 1982, Tans 1983, Kosteljanetz 1986, Kingman 1988). The clinical value of this new monitoring technique and the information it will reveal is still unclear, even though there is data that favors the concept that IC monitoring will yield valuable information in the treatment of patients with TBI.

AIMS

The aims of this study were:

1. To develop a rat TBI model for studies of intracranial pressure dynamics where intracranial compensatory volume could be reduced in a controlled fashion without raising ICP to pathological levels. (Paper I)
2. To determine if intracranial volume insults in the posttraumatic period led to increased metabolic disturbances, if IC was decreased. (Paper II)
3. To study whether transient hemorrhagic hypotensive insults in the post-traumatic period caused more secondary metabolic disturbances in the brain when IC was reduced. (Paper III)
4. To simultaneously monitor IC and cerebral metabolism in TBI patients, in order to get an impression of the clinical value of IC monitoring regarding the risk for development of secondary brain injury. (Paper IV)
5. To get an impression of the relationship between IC, temperature and L/P ratio in TBI patients and whether decreased IC affects the vulnerability of the brain for hyperthermia as reflected by interstitial biochemical changes. (Paper IV)

MATERIALS AND METHODS

Experimental studies

Animal procedures

For all experimental studies male Sprague-Dawley rats (320-570 g) were used. They had free access to food pellets and water. Anesthesia was induced by placing the rats in a gas mixture of Halothane® 3% and O₂:N₂O (1:1), followed by endotracheal intubation and mechanical ventilation. Anesthesia was maintained with isoflurane (1.2-1.8 %) and O₂:N₂O (1:2). Arterial and venous catheters were surgically implanted into tail vessels. Additionally a catheter was placed in the right femoral artery for blood withdrawal in animals scheduled for hemorrhagic hypotension (paper III). Mean arterial blood pressure and body temperature, were continually measured. Body temperature was monitored with a rectal probe and maintained constant at 37.5° C with a heating pad and a desk lamp at appropriate distance. Arterial blood gases were checked regularly. The animal was placed in a stereotaxic frame and the skull was exposed through a midline scalp incision. A burr hole (1.0-mm diameter) was made 1 mm caudal to bregma and 1.6 mm lateral to the midline for access to the left ventricle. Bilateral craniotomies (6x9 mm) were made over the parietal cortex; centered 3 mm caudal to bregma on the right side, slightly more caudal on the left side due to the ventricular burr hole. A spinal needle (24 gauge, outer diameter 0.55 mm) was stereotactically inserted into the left lateral ventricle for intracranial pressure (ICP) monitoring and volume-pressure response (VPR) injections/measurements. During insertion continuous registration of ICP was carried out. Intraventricular placement was confirmed by the sudden decrease in ICP upon ventricular puncture, a rapid increase in ICP due to jugular vein compression and the presence of cardiopulmonary pulsation on the monitor screen. For ICP recording the zero point was adjusted to the level of the external auditory canal. A two-way single lumen system (PK Kit IDT-XX, Ohmeda Pte Ltd, Singapore), filled with saline, was used for ICP measurements. The tubing system was in open communication between the syringe, left lateral ventricle and pressure transducer. An amplifier (Transducer Interface, Harvard Apparatus, Edenbridge, England) was connected to a computer running

LabWindows CVI software for continuous on-line acquisition, display and storage of the ICP signal. A microdialysis (MD) probe was inserted through a small incision in the dura medially in the perimeter of the trauma zone (right side). ICP recording and MD samples collected for 2 hrs followed in order to obtain MD baseline values. Figure 2 shows a schematic drawing of the surgical procedure.

At the end of the experiment the animals were perfusion fixated with formaldehyde. The brains were cut in coronal sections and analysed under the operating microscope.

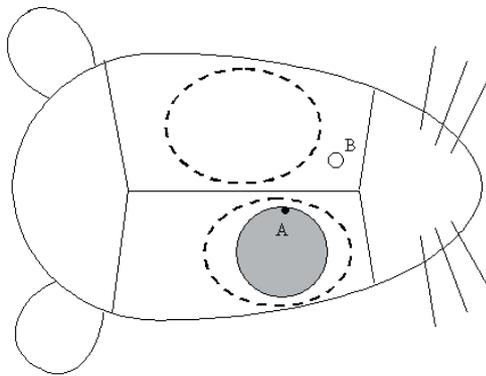


Figure 2. Schematic drawing of the rat head. Craniotomy defined by the dotted lines, trauma region by the shaded area. (A) Placement of microdialysis probe. (B) Burr hole for ventricular catheter.

TBI and reduction of intracranial compensatory volume

Trauma injury was induced by weight drop technique; 21 g weight from 35 cm onto a piston (diameter 4.5 mm) resting on the dura, allowing a maximum epidural compression of 1.5 mm (Feeney 1981, Nilsson 1990). In the sham injury groups the weight was not dropped, otherwise the surgical preparation was the same. From earlier work we knew that the degree of injury used causes release of excitatory amino acids, metabolic disturbances (Nilsson 1990, Nilsson 1994), Ca^{2+} and K^{+} shifts between extra/intracellular space (Nilsson 1993, Nilsson 1996), decreases in cerebral blood flow (Nilsson 1996), effects on behavior (Lewen 1999), morphological changes (Nilsson 1993, Lewen 1995, Lewen 1996, Lewen 1999) and blood brain barrier disturbances (Nilsson 1993).

Before the trauma, the ICP needle and the MD probe were removed. After the trauma the MD-probe and ICP-needle were stereotactically reinserted within 1 min and 3 min, respectively. Intracranial volume was altered by gluing 0, 1 or 3 layers of rubber film (0.18 mm thick; Kofferdamm medium, Dental AB, Stockholm, Sweden) on the inside of the bone flaps before they were glued back in place using Histoacryl (B Braun Melsungen, Germany) tissue glue for both procedures. One layer of rubber film constituted a volume of approximately 10 μ L. Figure 3 shows a side picture of the bone flap with 3 layers of rubber film. The bone flaps were replaced within 5-10 min after injury under microscopic control.

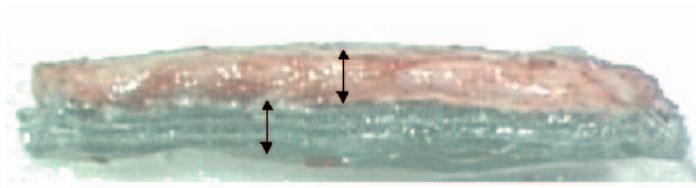


Figure 3. Side view (with a slight upward rotation) of bone flap (upper arrow) with three layers of rubber film (lower arrow).

Intracranial pressure volume dynamics (paper I and II)

30 animals divided into six groups (sham/trauma with 0/1/3 layers of rubber film, respectively) were used (n=5). Bolus injection technique was used for Volume-Pressure Response (VPR) measurements. Six bolus injections, each constituting of 50 μ L saline (0,9%), were done by hand using a 250 μ L Hamilton-syringe. The injection time was approximately 0.5 sec. The injections were done in two sets at time points 20, 30, 40 and 80, 90, 100 min after trauma/sham injury (see Figure 5). The time points were chosen in order to mimic a clinical situation and to facilitate the statistical analysis. In order to maintain adequate ICP recordings no withdrawal of saline was attempted between the injections.

Pressure-Volume Index (PVI), Intracranial Compliance (IC) and CSF Outflow Resistance (R_o) were calculated according to the injection bolus tech-

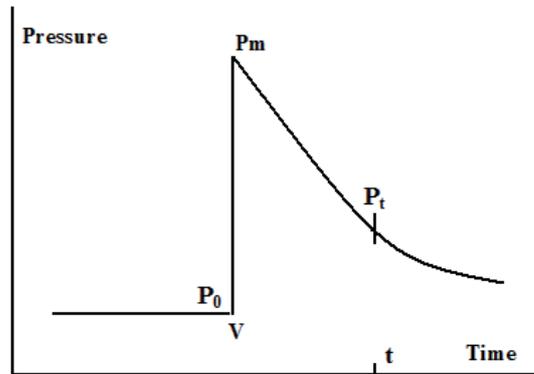


Figure 4. Schematic drawing of the VPR. P_0 -baseline ICP (mmHg), V -injected volume (mL), P_m - maximal ICP after injection, t - time after injection (min) and P_t - ICP at time t .

nique as described by Marmarou (Marmarou 1975) using the following equations:

$$PVI = \frac{V}{\log_{10}(P_m / P_0)} \quad \text{mL}$$

$$IC = \frac{V}{(P_m - P_0)} \quad \text{mL / mmHg}$$

$$R_o = \frac{t \times P_0}{PVI \times \log_{10}((P_t/P_m)(P_m-P_0)/(P_t-P_0))} \quad \text{mmHg / mL / min}$$

V = injected bolus-volume (mL); P_0 = baseline ICP (mmHg) prior to bolus injection; P_m = maximal ICP after bolus injection (mmHg); t = time after injection (min.) and was 1 minute in the present study; P_t = ICP at the time t after injection (mmHg); see Figure 4.

As mentioned in the introduction section the IC is directly proportional to the PVI at a given pressure according to the formulae: $IC = 0.4343 * PVI / P$ where P is the ICP at evaluation. Since we planned six injections at different times we chose to use the direct formulae for calculations of IC and PVI separately.

Intracranial volume insults (paper II)

The bolus injections performed in Paper I served as intracranial volume insults and the influence on the brain when IC was altered was analysed by evaluating the MD results. As mentioned above 6 bolus injections, each constituting of 50 μ L saline, were given. The sham and trauma groups with 0 and 3 layers of rubber film were compared. Animals without VPR injections from the subsequent experiment (hypotension study in paper III) were used as controls. The volume insults (injections) were given at the beginning of each corresponding 10-minute microdialysate sampling period. For statistical analysis the experiments were divided into four time periods. The impact period (20 min) including the first two 10 min fractions after the trauma followed by three 30 min periods: VPR_set 1 (covering first 3 VPR injections), VPR_inter (covering the period between first and last VPR injection period) and VPR_set 2 (covering the last 3 VPR injections). Figure 5 shows the experimental setup in paper II.

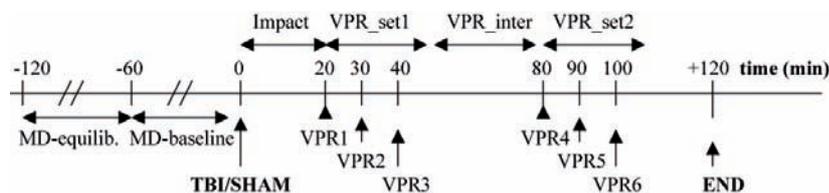


Figure 5. Flow chart of experiments. MD, microdialysis; TBI/sham, impact with traumatic brain injury or sham injury; VPR 1 to 6, volume pressure response injections (i.e., volume insults). Time periods: impact, VPR_set1, VPR_inter, VPR_set2.

Hypotensive insult (paper III)

A total of 32 animals divided into four groups (sham/trauma with 0/3 layers of rubber film) were used (n=8). All animals were subjected to hypotension that was induced by withdrawal of blood through the femoral artery. To mimic clinical ICU conditions we chose a time point (two hours post-trauma/sham) when metabolic conditions had normalized after the trauma (Nilsson 1990, Nilsson 1993). We also used a relative moderate and controlled hypotensive insult, 50 mmHg for 30 min, since the most likely hypotensive

insult occurring in TBI patients during the ICU period is a mild-moderate transient hypotension (Winchell 1996).

Heparanised syringes were used to draw blood until the MABP reached approximately 50 mmHg and maintained at this level for 30 min by further withdrawal of blood or reinjection of blood as needed. Normally 5-8 mL blood withdrawal was required to obtain MABP of 50 mmHg. The blood was kept warm (37 °C). After 30 min of hypotension, reperfusion started with slowly reinjection of blood as required to obtain normal MABP. Figure 6 shows the experimental setup in paper III. For statistical analyses the experiment was divided into five time periods: (T1) 30 min before trauma (baseline period), (T2) 30 min after trauma (trauma period), (T3) 30 minutes before hypotension (preinsult period), (T4) 30 min hypotensive insult (insult period) and (T5) 30 min after insult (reperfusion period).



Figure 6. Flowchart for the hypotension study. Time periods T1-T5.

Microdialysis (paper I-III)

A MD probe (MAB 6.14.2, membrane length 2 mm; Metalant AB, Stockholm, Sweden) was stereotactically inserted through a small incision in the dura medially on the right side in the perimeter of the trauma zone. Probes were placed identically in both sham and injured animal groups. Mock CSF (containing Na⁺ 140mM, K⁺ 2.7mM, Ca²⁺ 1.2mM, Mg²⁺ 0.9mM and Cl⁻ 147mM) was perfused through the probe at a flow rate of 2 μL/min using a microinjection pump (CMA/100, CMA/Microdialysis, Stockholm, Sweden). After 1 h of equilibration the MD samples were collected in 10-min fractions

for 1hr before trauma and the last three 10-min fractions were averaged to obtain a baseline value.

The analyses were randomly performed. Analyses of energy metabolites (lactate, pyruvate, and hypoxanthine) were made in order to assess the metabolic state. Glycerol was analyzed as a marker of cell membrane degradation. Lactate, pyruvate and glycerol were analysed with an enzymatic colorimetric method using the CMA/600 microdialysate analyzer (CMA Microdialysis, Stockholm, Sweden). Hypoxanthine was measured using high performance liquid chromatography.

Clinical study

Patients

Ten TBI patients (nine males and one female) admitted to our unit were included in this study. Patient characteristics are shown in table 1. The median age was 54 years (range: 19-63). Eight out of ten patients underwent primary investigation and resuscitation in local city hospitals before transfer to our unit. The mean GCS on admission to our unit was 7 (range: 4-10). Eight out of ten patients had a GCS \leq 8. Median injury severity score (ISS) (Baker 1976) was 18 (range: 9-45). CT classifications were made on the first CT scan performed on each patient, according to the Traumatic Coma Data Bank (TCDB) categories (Marshall 1992). Six patients presented with diffuse injury (DI) type 2, three patients with DI type 3 and one patient with DI type 2 and a small epidural hematoma that did not require surgical removal. After arrival to the NIC unit, the patients were transferred to the operating theater where an ICP monitor and MD probe were placed. One patient developed a focal mass lesion (large frontal contusion) four days after injury that required surgical removal (case 6). Two patients without focal mass lesions underwent barbiturate coma treatment due to refractory high ICP. One patient who developed seizures and refractory status epilepticus was treated with midazolam coma (Dormicum®, Roche).

Table 1. Demographic and injury characteristics of TBI patients

Patient	Age (yrs)	GCS	ISS	CT class	IC start	Monitoring time (hrs)	Coma treatment	Surgery	GOSE
1	53	8	16	DI 2, t-sah	< 1 d	130	No	No	lost f-up
2	34	4	45	DI 3	< 1 d	98	Yes	No	SD lower
3	55	7	29	DI 3, t-sah	5 d	63	Yes	No	dead
4	58	8	9	DI 2, t-sah	< 1 d	40	No	No	GR
5	63	8	16	DI 2, EDH (<25cc)	< 1 d	68	Yes	No	MD upper
6	58	10	25	DI 2, t-sah	3 d	105	No	Yes day 4	MD lower
7	19	5	16	DI 2	< 1 d	58	No	No	GR
8	32	4	25	DI 3	< 1 d	98	No	No	dead
9	23	7	18	DI 2	2 d	52	No	No	MD upper
10	56	10	18	DI 2, t-sah	< 1 d	84	No	No	GR

GCS: (Glasgow Coma Scale) on admission, ISS: (injury severity score), CT class: CT-findings according to the traumatic coma data bank categories (DI = diffuse injury; t-sah = traumatic subarachnoid hemorrhage; EDH = epidural hematoma), IC start: start of intracranial compliance monitoring, GOSE: (Extended Glasgow outcome scale) at six months.

Neurosurgical intensive care

The management protocol for severe TBI patients in our unit has been described earlier (Elf 2002). Briefly it includes intubation of all unconscious patients ($GCS\ M \leq 5$) (or patients judged to be at high risk of impairment) and slight hyperventilation ($PaCO_2$ 4.0-4.5 kPa) initially. Normal arterial blood pressure, ICP (≤ 20 mmHg), CPP (~ 60 mmHg), central venous pressure (CVP) (0-5 mmHg) and $PaO_2 > 12$ kPa. Temperature was continuously measured in the urinary bladder. ICP-monitoring in all patients not responding to commands. Continuous EEG recording in selected cases. Regular checks of arterial blood gases and blood glucose. Regular assessment and recording of neurological state (GCS), pupillary function and focal neurological signs. Patients undergo a repeat CT within 48 hrs after admission or immediately if ICP is increased or if neurological deterioration occurs. Evacuation of focal mass lesions when necessary. If raised ICP levels do not resolve on ordinary treatment as summarized, patients are given barbiturate treatment, which begins with repeated 50 mg injections iv until ICP has decreased, followed by a continuous infusion of thiopental (Pentothal®Natrium, Abbott Laboratories, Abbot Park, IL). The thiopental dose is adjusted to the lowest dose required to maintain ICP < 20 mmHg, normally 2-6mg/kg/hr, but not necessarily to burst suppression. CPP ≥ 50 mmHg is accepted during barbiturate coma treatment.

Intracranial compliance monitoring

ICP and IC were monitored with an intraventricular Spiegelberg catheter connected to the Spiegelberg Compliance Monitor (Aesculap®, Tuttlingen, Germany) (Spiegelberg 1996). Using the same principle as a regular ventricular catheter routinely used in clinical practice for ICP monitoring, the Spiegelberg Compliance Monitor measures ICP and calculates IC/PVI by repeatedly adding and extracting 0.2 mL of air into a *double lumen intraventricular balloon catheter*. The monitor cyclically adds the volume and extracts it 2.5 seconds later. The small pressure changes resulting from the volume perturbations are made measurable by an averaging method from 20 up to 200 volume addition/removal cycles, according to the level of disturbance. The IC is calculated from the averaged pressure differences and the PVI is directly calculated from the IC and the mean ICP according to Marmarous equation (Marmarou 1975). The device produces a minute by minute measure of IC and PVI once a stable average has been obtained which updates each minute from a moving window average.

Data were collected every minute as long as the patients were in the NIC unit. Eight patients received the Spiegelberg catheter within 24 hrs from injury. One of these patients had bilateral tibia fractures that were treated surgically so the IC monitoring was delayed and started on day two after injury. The other two patients initially received an intraparenchymatous ICP-monitoring probe (within 24 hrs from injury) due to compressed ventricles. The parenchyma probe was replaced by an intraventricular Spiegelberg catheter when the ventricles had enlarged on day 3 and 5, respectively. Correct intraventricular catheter placement was confirmed with a CT scan. Mean monitoring time was 80 hours (range: 40-130).

Microdialysis

A MD-probe (CMA/70, 10 mm membrane length, CMA Microdialysis, Stockholm, Sweden) was inserted into the frontal cortex through a separate burr hole located close to the ICP monitoring device. The probe was perfused with artificial CSF at a rate of 0.3 $\mu\text{L}/\text{minute}$. Hourly dialysate samples were analyzed bedside on a CMA/600 microdialysate analyzer with an enzymatic colorimetric method (CMA Microdialysis, Stockholm, Sweden).

Data collection and follow up

Surveillance data (heart rate, respiratory rate, BP, ICP, CPP, IC, PVI, temp, O_2 saturation) was stored on a minute by minute basis and could be reached for analyses and validation using special software, The Browser (Howells 1995). GOSE at six months was used as follow up endpoint.

Statistical methods

In *paper I* comparisons were performed using Linear Mixed Effects models, as implemented in S-Plus 6.0 (Insightful, Inc.). Treatment-group and numbers of layers of rubber were included as factors in each ANOVA-model and time was included as a continuous covariate. Models with the two-way and three-way interactions were also fit. Time was modeled both as a fixed and a random effect. Repeated measurements ANOVA was used *in paper II* to test

for differences (between all trauma groups and between all sham groups) in lactate, LP ratio, hypoxanthine, and glycerol within each period. The trauma and sham groups were compared separately. In *paper III* the averages for each rat and time period were analysed in an ANCOVA (analysis of covariance) model including the factors: group (the four groups S0H, S3H, T0H, T3H), time, case nested within time and the interaction time by group. ICP was included as a covariate in analyses of all variables except ICP. The significance of each main effect and the pair wise comparisons between groups and time periods were derived from the model. The procedure GLM in SAS[®] version 9.1 was used for the analyses.

In *paper IV* formal modeling was performed using the M1wiN program version 1.2 (Multilevel Models Project, Rashbash, Browne, Mealy, Cameron and Charleton, 2002). Three models were fit. In the first two models, the individual relationships between compliance and L/P ratio, and temperature and L/P ratio were fit to examine relationship of each of the physiologic variables separately. Based on the explanatory analysis a polynomial was used to describe the physiologic measures. The presence of coma treatment at the time was included, and a coma treatment by physiologic measure interaction was added. The third model examined the combined effects of temperature and compliance on L/P ratio. The interaction of temperature and compliance was fit.

In all papers the tests were two-sided and $P < 0.05$ was considered as statistically significant. All analyses should be regarded as hypothesis-generating, hence no adjustments for multiplicity were made.

Ethics

All experimental protocols were approved by the Ethical Committee on Animal Experiments. The clinical study was approved by the Regional Ethical Review Board in Uppsala.

RESULTS

Experimental studies

Physiological parameters and macromorphology

Physiological parameters were checked and maintained at normal levels: $p\text{CO}_2 \sim 5$ kPa, $p\text{O}_2 \sim 15$ kPa, $\text{pH} \sim 7.40$, $\text{MABP} \sim 80\text{-}90$ mmHg and temperature ~ 37 °C. In animals subjected to hemorrhagic hypotension blood gases could not be checked during the hypotensive insult or reperfusion periods, due to practical reasons. Inspection of the perfused brains under the operating microscope revealed no signs of hematoma. In animals subjected to repeated intraventricular volume injections a slight ventricular dilatation could be noted (Paper I and II).

Animal model (paper I)

This study showed a consistent reduction in PVI related to the number of rubber film layers inserted between the dura and the bone flaps in both the trauma and sham operated animals. The baseline ICP prior to first VPR measurement was not significantly different between the groups. Table 2 shows baseline ICP and the calculated results at first VPR measurement.

Even though baseline ICP was not significantly different between the groups and stable prior to each VPR, statistics for all six VPR measurements revealed that ICP increased significantly with time (i.e. with each injection) ($p < 0.001$). The slope of the increase was greater for the trauma groups than for the sham groups at a given number of layers ($p = 0.0098$), but the slopes also depended on the number of layers of rubber ($p = 0.003$), where the ICP slope for zero layers was greater than for one layer which is greater than that for three layers. Figure 7 contains a graphical representation of the data.

Table 2. Baseline ICP, PVI, Compliance and R_0 at first measurement.

Injury	Rubber layers	N	ICP prior to VPR 1 mmHg	PVI at VPR 1 mL	IC at VPR 1 mL/mmHg	R_0 at VPR 1 mmHg/mL/min
			Mean \pm S.D.	Mean \pm S.D.	Mean ¹ \pm S.D.	Mean \pm S.D.
Sham	0	5	8.7 \pm 0.76	0.0825 \pm 0.009	1.587 \pm 0.603	487.4 \pm 151.3
Sham	1	5	9.4 \pm 2.08	0.0728 \pm 0.023 ^a	1.555 \pm 0.520	414.0 \pm 161.8
Sham	3	5	10.2 \pm 2.82	0.0779 \pm 0.011 ^a	1.386 \pm 0.388	493.4 \pm 364.3
Trauma	0	5	10.1 \pm 1.03	0.0871 \pm 0.018	1.531 \pm 0.600	540.4 \pm 74.5
Trauma	1	5	8.8 \pm 1.16	0.0668 \pm 0.000 ^b	1.408 \pm 0.352	439.7 \pm 96.9
Trauma	3	5	8.7 \pm 1.20	0.0748 \pm 0.013 ^b	1.388 \pm 0.413	584.4 \pm 151.1

¹ $\times 10^{-3}$, ^a significant difference to sham 0 layers, ^b significant difference to trauma 0 layers.

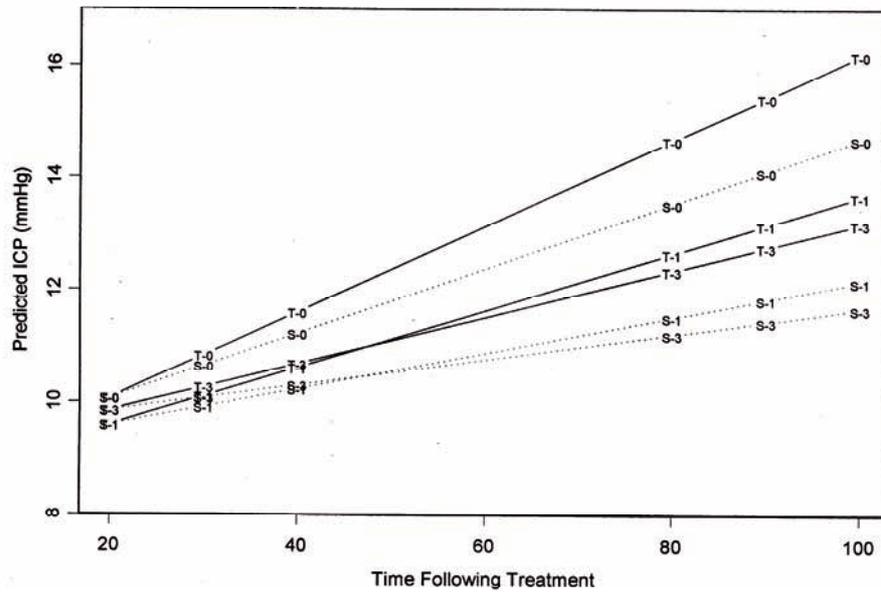
A significant difference in PVI among the three layers was found ($p=0.0150$), with a consistent reduction in PVI related to increasing number of layers but also a significant increase in PVI over time ($p = 0.003$). There was no difference between the sham and trauma groups ($p=0.9191$) nor were there any indications that the rate of change in PVI over time depended on the treatment group or number of layers. The mean PVI predicted by the model is shown in figure 8 and table 3.

Table 3. Predicted PVI at 60 min following injury

Group	Predicted Average PVI
0 Layers	0.0891
1 Layer	0.0826
3 Layers	0.0782

Intracranial compliance differed depending on the number of layers, with a reduction related to increased number of layers even though not statistically significant in our model. The only significant finding from the modeling of compliance was a significant decrease with time after injury ($p<0.002$). These results are illustrated in figure 9. CSF outflow resistance (R_0) showed a significant increase with time after injury ($p<0.001$), otherwise there were no significant differences, see figure 10.

Results of Model Fitting for ICP



Results of PVI Modeling

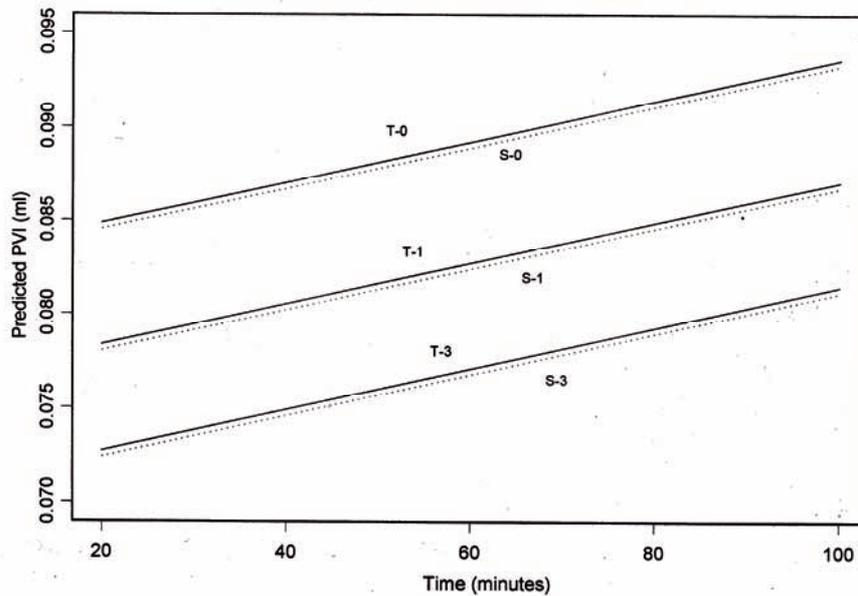
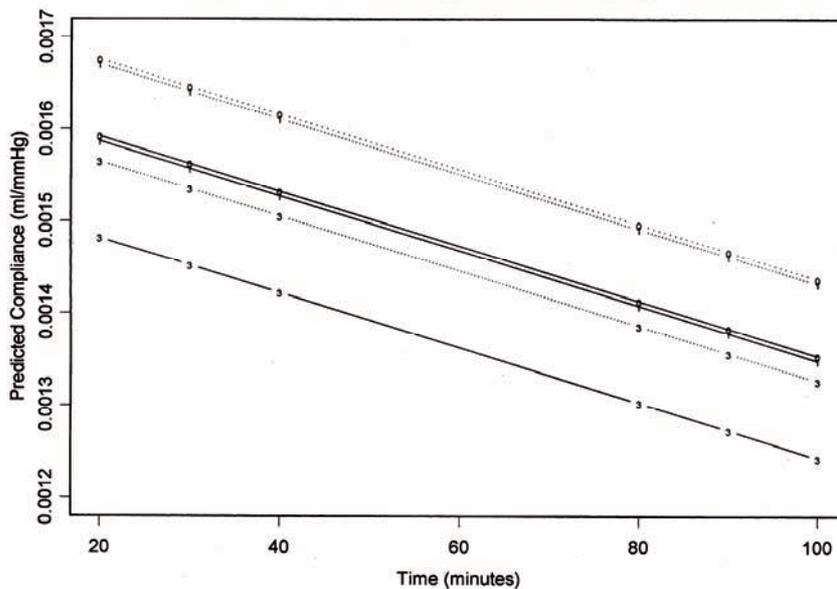


Figure 7 (upper) shows results of model fitting for ICP and Figure 8 (lower) shows results for PVI modeling.

Results of Compliance Modeling



Results of R_0 Modeling

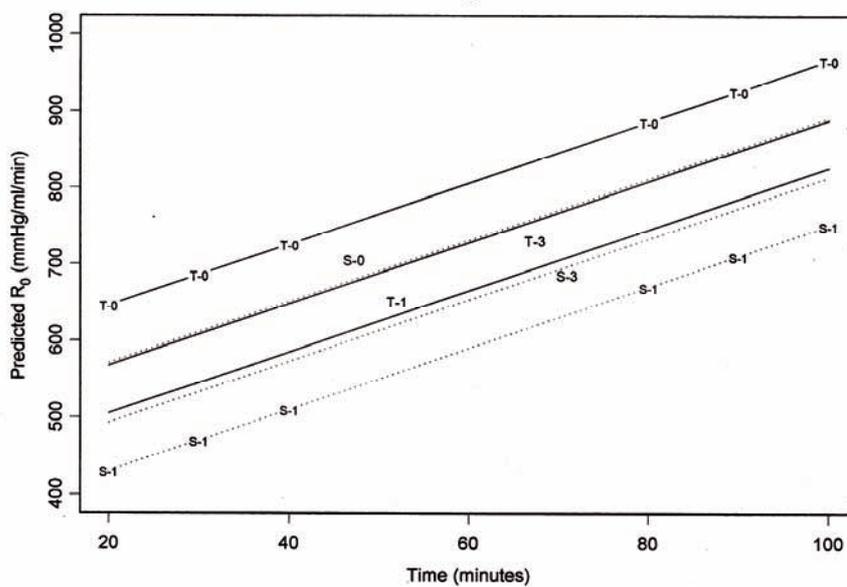


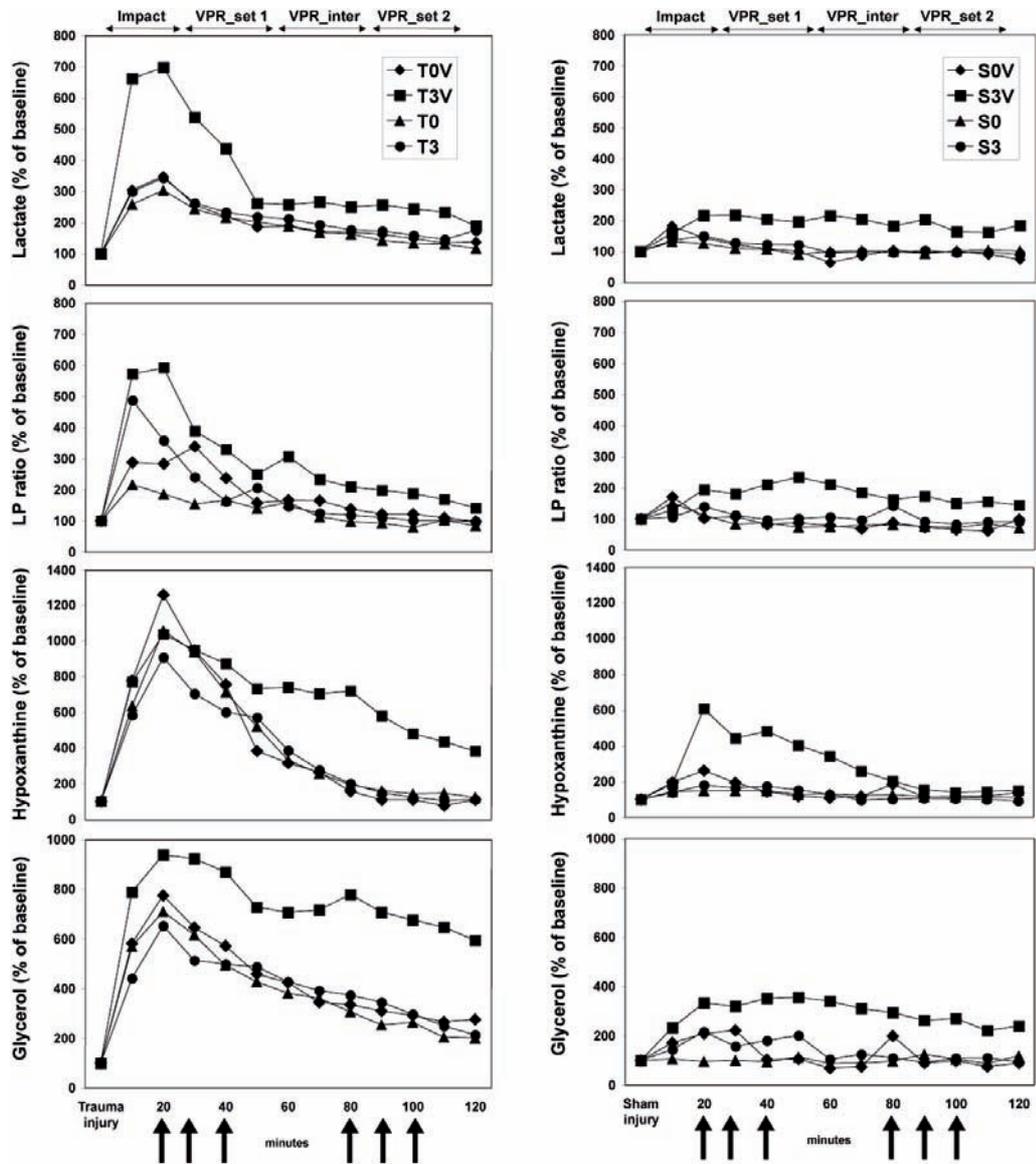
Figure 9 (upper) shows results of compliance modeling and *Figure 10* (lower) shows results of R_0 modeling.

Effect of intracranial volume insults (paper II)

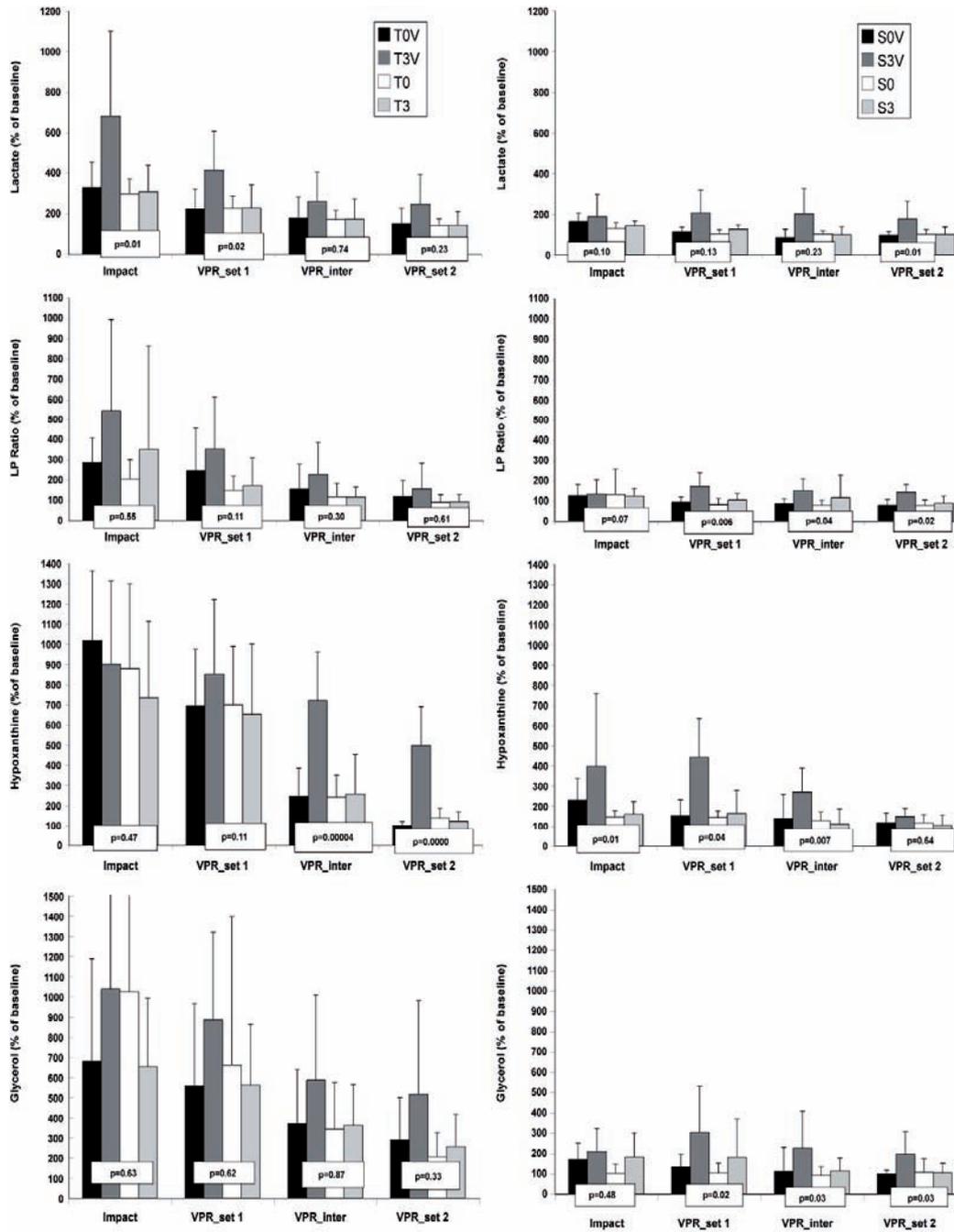
In this study the aim was to see whether intracranial volume insults in the posttraumatic period led to increased metabolic disturbances (measured with MD) if IC was decreased. Trauma and sham injury groups were compared separately. Figure 11 shows the peak value and temporal pattern and figure 12 the corresponding values for the different time periods with p-values, in the trauma injury groups. Figures 13 and 14 shows the corresponding values for the sham injury groups.

The mean values for groups T0 (trauma injury, 0 layer, no volume insult), T0V (trauma injury, 0 layer and volume insult) and T3 (trauma injury, 3 layers and no volume insult) showed an almost identical peak and temporal pattern. Group T3V (trauma injury, 3 layers and volume insult) was different from the other trauma groups in that peak values were slightly higher for lactate, L/P ratio and glycerol. The temporal pattern was also different in this group for all measured metabolites except LP ratio, with a prolonged increase and a slower decrease slope than for the other groups. Statistics within the time periods (figure 12) showed that group T3V had significantly higher lactate levels during the impact and VPR_set 1, and significantly higher hypoxanthine during the VPR_inter and VPR_set 2. Even though there is a clear tendency of higher dialysate levels for lactate and glycerol during the latter time periods these changes were not statistically significant.

In the sham injury groups (see figures 13 and 14) the only notable change was for group S3V (sham injury, 3 layers and volume insult), with a slight increase for all dialysates. When comparing time periods only group S3V shows significant changes with lactate increased during VPR_set 2, LP ratio and glycerol increased for all periods except for the impact period, and hypoxanthine significantly increased for all periods except the last one (VPR_set 2).



Figures 11 (left) and 13 (right). Temporal pattern for the trauma and sham injury groups. Mean percentage values as compared to baseline. Arrows indicate time points for VPR (volume pressure response) injections (groups TOV/T3V and S0V/S3V respectively). Group definitions: T/S = trauma /sham, 0/3 = number of layers, V= VPR injection.



Figures 12 (left) and 14 (right). Average values for each time period (mean \pm S.D.) in trauma and sham injury groups, respectively. P-values shown for each period. See figure 11 and 13 for group definitions.

Effect of hemorrhagic hypotension (paper III)

Figures 15-20 and table 4 contain the overall results of the analyses for BP, ICP and each of the measured dialysates (lactate, LP Ratio, hypoxanthine and glycerol). The time effect (indicating that there are significant changes in measures of all groups as a function of time) and the group by time effect (indicating that the difference between the groups depended on time) were the most commonly significant results. For ICP this was mainly due to a layers-time interaction and for the dialysates mainly due to an injury-time interaction. Table 5 shows p-values for comparisons within and between groups for different time periods (all time periods not shown).

Table 4. Probability values for the different effects.

Dependent	Group	Time	ICP	Group*Time
Blood Pressure	0.4821	<.0001	0.0929	0.0689
ICP	0.1577	<.0001	-----	0.0464
Log LP-ratio	0.2774	<.0001	0.1229	0.0007
Log Glycerol	0.6700	<.0001	0.8954	0.0108
Log Hypoxanthine	0.0971	<.0001	0.0418	<.0001
Log Lactate	0.1871	<.0001	0.4357	<.0001

The hypotensive insult was significant for all groups (figure 15 and table 5). During the hypotensive insult there was a consistent and significant decrease in ICP for all groups compared to the pre-insult period (figure 16 and table 5). The reperfusion resulted in the subsequent return to or slight overshoot of preinsult ICP levels. The effect of hypotension on ICP was the same for all groups.

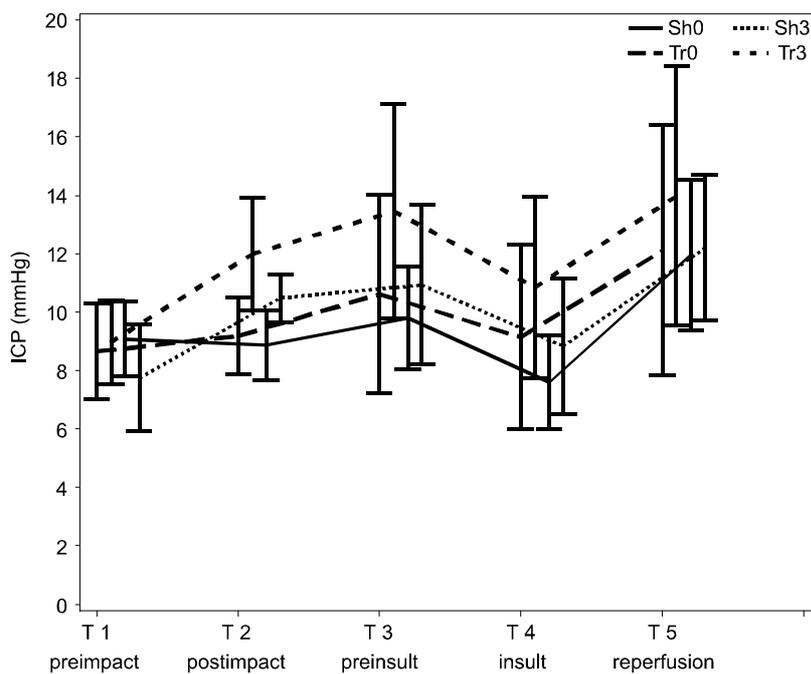
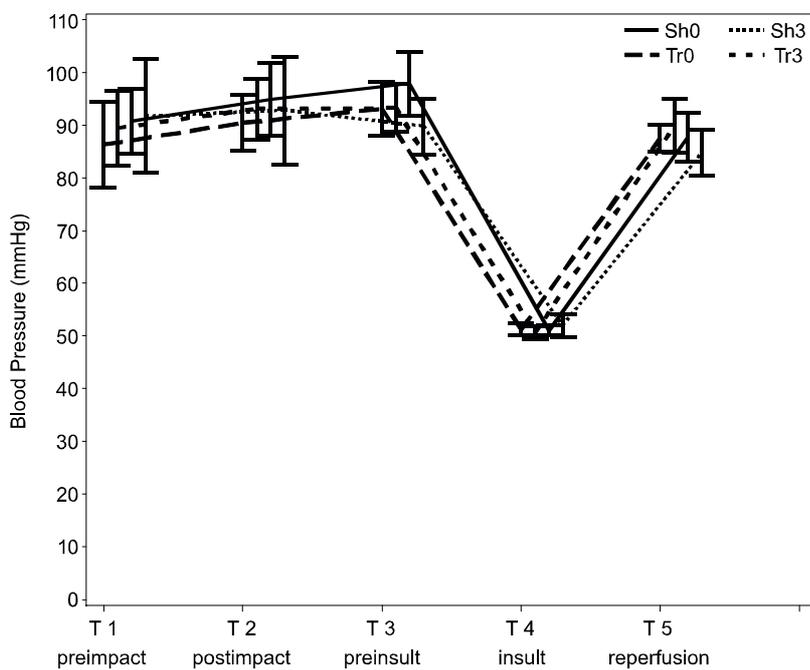


Figure 15 (upper) and **Figure 16** (lower). Blood pressure and ICP. Averaged values for time periods (mean \pm S.D.).

There were only minor neurochemical changes induced by the hypotensive insult (figures 17-20). Compared to preinsult values, statistics showed a slight increase in LP-ratio for group Sh3 that normalised during reperfusion and a slight increase in lactate for all groups reaching significance for all except Tr3 and this increase remains during reperfusion as compared to pre-insult period. For the other dialysates no significant effects were seen. There were no obvious effects related to layers (e.g. compliance level) during the insult or reperfusion periods.

Table 5. Comparisons within and between groups

	Blood					
	Pressure	ICP	Lactate	LP-ratio	Hypoxanthine	Glycerol
T2-T1, Sh0	0.0788	0.7773	0.0807	0.9197	0.0152	0.0555
T2-T1, Sh3	0.3047	0.0004	0.0036	0.4605	0.0007	0.0525
T2-T1, Tr0	0.0489	0.4717	<.0001	0.0001	<.0001	<.0001
T2-T1, Tr3	0.0315	0.0001	<.0001	<.0001	<.0001	<.0001
T2-T1, Sh3-Sh0	0.6418	0.0060	0.3438	0.5463	0.3964	0.9238
T2-T1, Tr0-Sh0	0.8761	0.4785	<.0001	0.0065	<.0001	0.0005
T2-T1, Tr3-Sh3	0.3818	0.7826	<.0001	0.0001	<.0001	0.0009
T2-T1, Tr3-Tr0	0.8159	0.0198	0.6115	0.3985	0.4634	0.9520
T4-T3, Sh0	<.0001	0.0034	0.0423	0.2167	0.6306	0.6375
T4-T3, Sh3	<.0001	0.0055	0.0010	0.0145	0.5647	0.3480
T4-T3, Tr0	<.0001	0.0487	0.0092	0.5055	0.6444	0.6548
T4-T3, Tr3	<.0001	0.0006	0.5051	0.9506	0.1772	0.4177
T4-T3, Sh3-Sh0	0.0040	0.9094	0.3348	0.3668	0.4366	0.7324
T4-T3, Tr0-Sh0	0.0888	0.4823	0.6926	0.6669	0.9819	0.5052
T4-T3, Tr3-Sh3	0.1017	0.6286	0.0504	0.0650	0.1522	0.1980
T4-T3, Tr3-Tr0	0.6699	0.2843	0.1640	0.6011	0.5595	0.7783

T1-T4 = time periods. Sh/Tr = sham or trauma injury. 0/3 = number of layers. P-values from contrasts in ANCOVA-model.

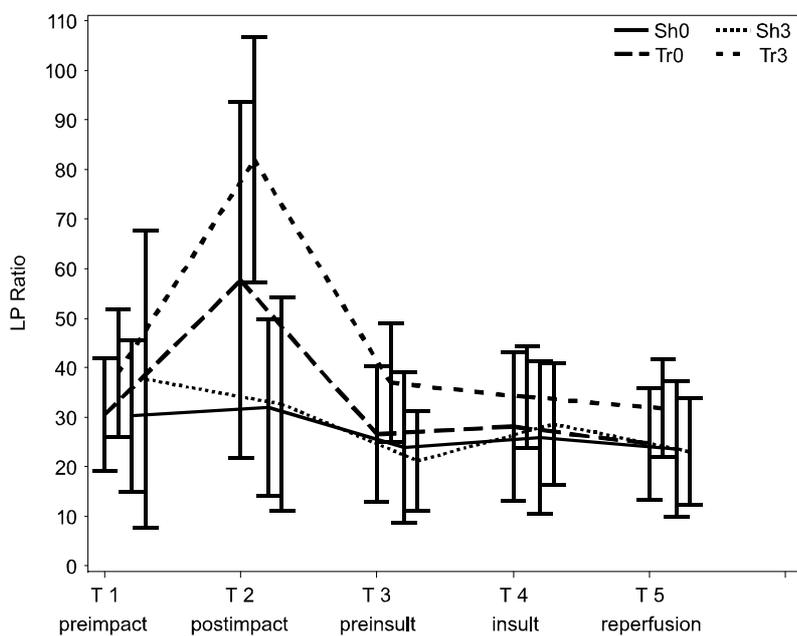
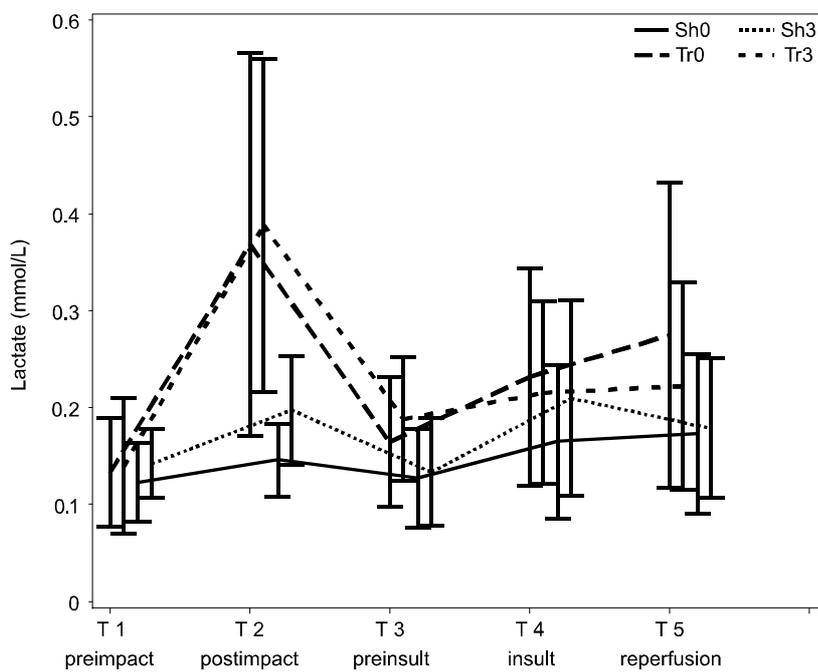


Figure 17 (upper) and **Figure 18** (lower). Lactate and LP ratio. Averaged values for time periods (mean \pm S.D.).

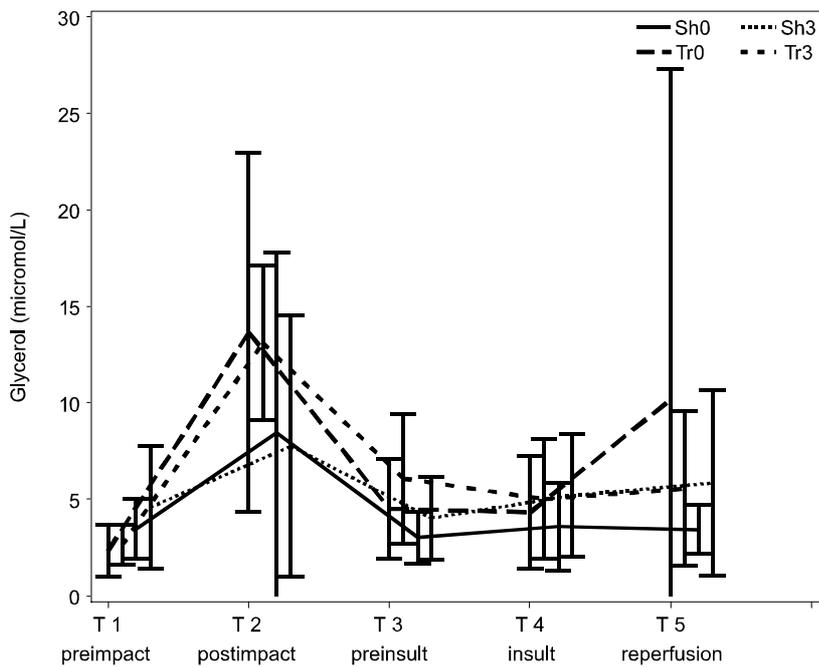
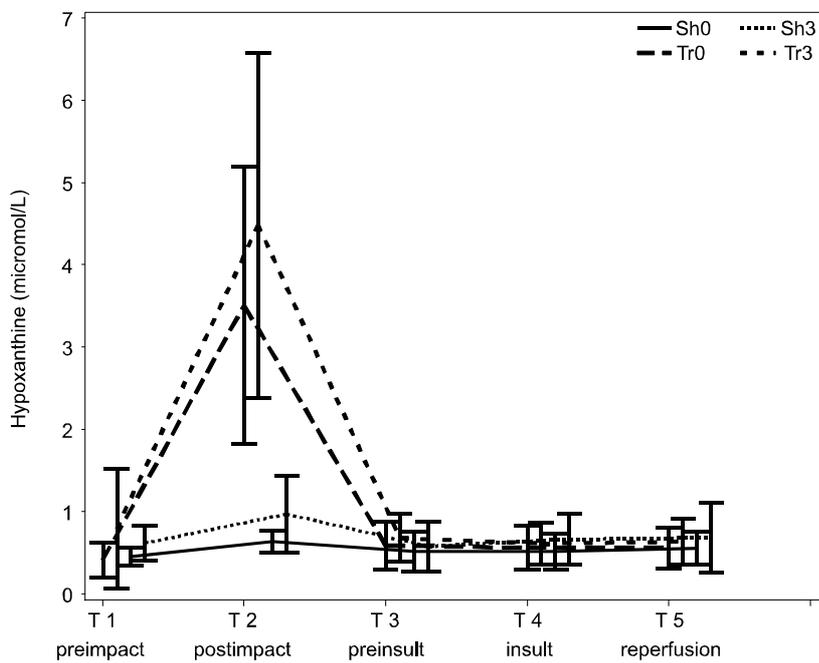


Figure 19 (upper) and Figure 20 (lower). Hypoxanthine and glycerol. Averaged values for time periods (mean \pm S.D.).

Clinical study

The statistical model of L/P ratio to compliance and coma treatment, showed significant effects due to compliance ($P < 0.0001$), coma treatment ($P = 0.006$) and the compliance by coma treatment interaction ($P < 0.0001$). The compliance effect indicates that a lower IC was associated with a higher L/P ratio. The coma effect indicates that the induced coma treatment patients had higher L/P ratio. The compliance/coma interaction indicates that the compliance effect on L/P ratio was different in the two groups of patients. Overall, there were significant polynomial relationships as illustrated in figure 21. The patients with coma treatment, upper plot, have higher L/P ratios, and tend to have lower compliance (as seen by the shift of the plot to the left). Their L/P ratios tend to rise and then fall as their compliance lowers. The patients without coma treatment have a rise in L/P ratio as compliance decreases towards 1.4 mL/mmHg, followed by a small fall as compliance lowers towards 0.90 mL/mmHg and then remains virtually unchanged with further compliance decrease.

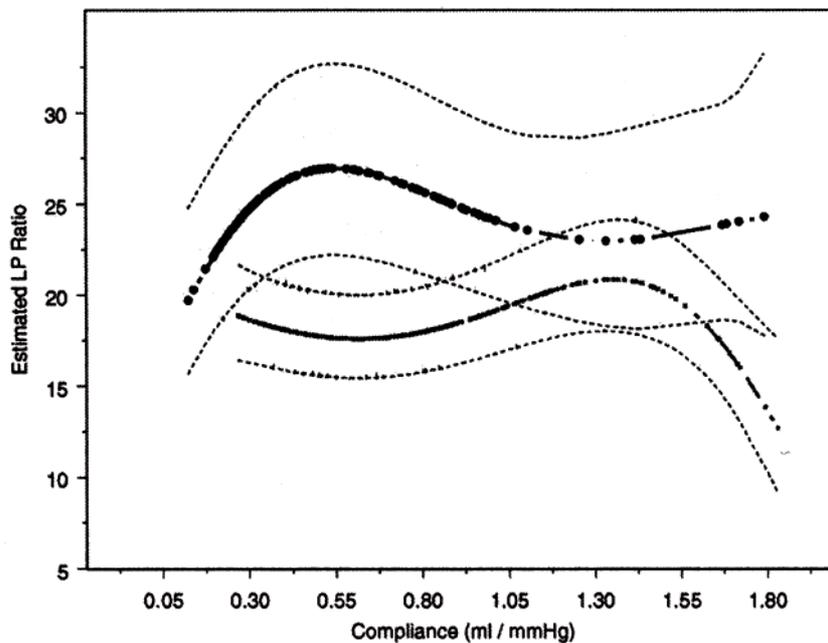


Figure 21. Results of model 1 for intracranial compliance and LP ratio. Patients with coma treatment (upper plot \pm SE) have higher LP ratio and tend to have lower compliance compared to the patients without coma treatment (lower plot).

The results from model two of L/P ratio to temperature and coma treatment showed a significant temperature effect ($P=0.0045$), no effect due to coma treatment ($P=0.18$) but significant effect of coma treatment by temperature interaction ($P=0.0080$), indicating the temperature effect was different in the two types of patients. Figure 22 illustrates these results: the shape of the relationship in patients with coma treatment (upper plot) is markedly different than the patients without coma treatment. In general, the effects seen in this temperature model were not as strong as those seen in the compliance model.

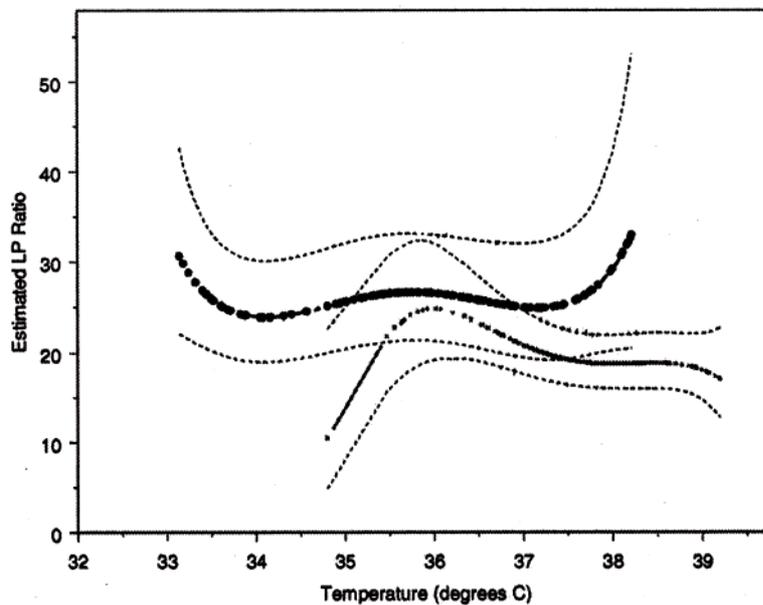


Figure 22. Results of model 2 for temperature and LP ratio. Coma treatment patients (upper plot \pm SE) and none coma treatment patients (lower plot). No clear differences were seen between the groups.

A third model, based on the two models mentioned above, examined the combined effects of temperature and compliance on L/P ratio. This model contained the quintiles of temperature and compliance (table 6), coma treatment, the interaction of coma treatment with the two physiologic variables and the interaction of temperature with compliance.

The results are summarized in table 7. The temperature by compliance interaction is the strongest finding in this model. This is easier to see in the patients with coma treatment (illustrated in figure 23) though there are fewer of these patients than patients without induced coma treatment (figure 24). In patients with high temperatures, the L/P ratio clearly rises as compliance decreases, but in patients who are cool, there is no effect of compliance. The

illustrative figures from model 3 were separated depending on coma treatment or not, even though the three-way interaction (between coma treatment, compliance and temperature) was not included in the model due to the small number of patients.

Table 6. Quintiles used in model 3

Quintile	Temperature Range	Compliance Range
1	33.1 - 36.3	0.1217 – 0.4014
2	36.4 - 37.2	0.4015 – 0.5294
3	37.3 - 37.7	0.5295 – 0.6942
4	37.8 - 38.1	0.6943 – 0.8975
5	38.2 - 39.2	0.8976 – 1.8320

Table 7. Results from model 3

Parameter	p-value
Coma	0.01985
Compliance	0.1969
Temperature	0.3196
Compliance by Coma Interaction	0.01030
Temperature by Coma Interaction	0.4829
Compliance by Temperature Interaction	<0.0001

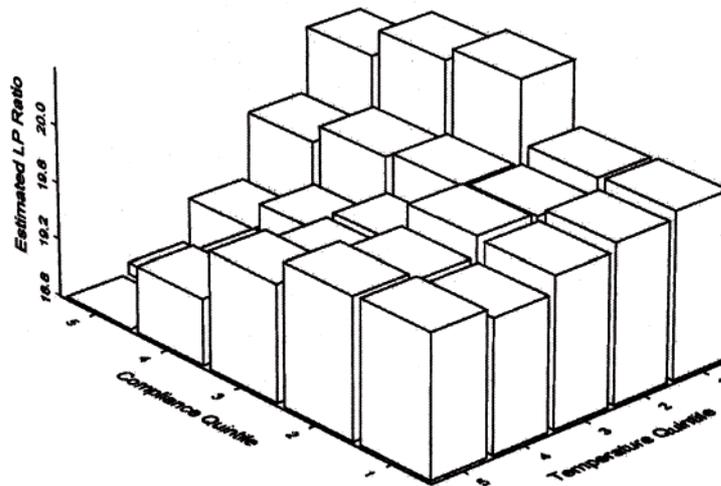


Figure 23. Model 3 with relationship of compliance and temperature to LP ratio in the coma treatment patients. The graph illustrates that for patients with high temperature LP ratio rises when compliance decreases but in patients with lower temperature there is no effect of compliance.

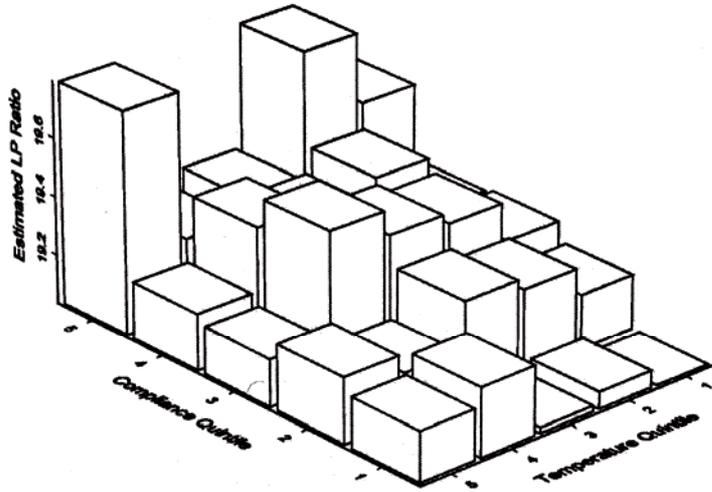


Figure 24. Model 3 with relationship of compliance and temperature to LP ratio in the group of patients without coma treatment. No obvious patterns depending on compliance and temperature were seen.

DISCUSSION

ICP monitoring is central in the care of severe TBI patients. The Spiegelberg Compliance Monitor (Spiegelberg 1996) offers a technical possibility to monitor IC in addition to ICP. The clinical relevance of IC monitoring is presently unclear, but information about where the patient is on the intracranial pressure volume relationship curve may be important in predicting vulnerability for secondary insults as well as the risk of developing high ICP. An increased understanding of the role of slightly reduced IC after TBI and the effect of different insults is warranted. The experimental model developed in this thesis was meant to serve as an experimental trauma model where it was possible to alter intracranial compliance and PVI in a controlled fashion without raising ICP to pathological levels. The experimental model could then be used to test the effects of secondary insults, at different levels of compliance, on e.g. metabolic disturbances, histology and behavior. By applying microdialysis, secondary brain injury could be studied in terms of neurochemical changes.

Validation of animal model (paper I)

An important feature of the model was the proven gradual reduction in PVI between 0, 1 and 3 layers of rubber film (figure 8). The difference between the number of layers was significant in both the trauma and control groups. These results would suggest that each layer of rubber film cause a stepwise shift in the pressure volume curve. The initial ICP level was not significantly different between the groups and were not higher than those reported by others as normal for the rat. In those studies ICP had been measured in the subarachnoid space (Mann 1978), in the lateral ventricle (Kingman 1988, Zwienerberg 1999) and in the cisterna magna (Botel 1994). Even though ICP never increased to abnormal levels, ICP increased significantly with time (figure 7). This increase was greater for the trauma groups compared to corresponding sham groups. It was also dependent on the number of layers, where the increase slope was greatest for zero layers and smallest for three layers. This increase in ICP over time may be caused by the VPR injections and may be related to increased outflow resistance (figure 10). The groups with zero

layers of rubber film have the highest increase in ICP and the highest CSF outflow resistance. One possible explanation for this result may be related to the surgical technique. The Histoacryl glue probably have a more direct contact with the underlying dura at the edge of the flap when there is no underlying layer of rubber film, which may cause a subsequent mechanical obstruction of the underlying subarachnoid space and venous outflow.

The volumes added to the intracranial space by the epidural rubber film were approximately 20 or 60 microliters in our study. This is equivalent to the volumes used by Kingman and colleges in their study with intracerebral mass lesions mimicking intracerebral hematomas (Kingman 1988). They reported an increase of ICP between 3-4 mmHg for added volume of 25-50 microliters, which is in line with our results. The trauma used in our model does not result in any additional large intracranial masses (i.e. hemorrhages) (Nilsson 1990). The reason for the relatively small effect on ICP caused by the 20-60 microliter extra volumes was probably a compensatory reduction in intracranial CSF and venous volumes, respectively (Langfitt 1969, Miller 1975b).

The PVI values in our study were within the range reported by other groups (Melton 1984, Botel 1994, Morimoto 1996). However, a direct comparison with those studies was difficult to make since ICP was measured in the cisterna magna. The compliance values obtained in our study did not show significant differences between the layers, even though there is a consistent reduction with the addition of layers (table 2 and figure 9). The levels themselves are difficult to corroborate since compliance has not previously been studied in the rat. An unclear result from the present study is the divergence over time between PVI and compliance (figures 8 and 9). One would expect that compliance and PVI should both increase or decrease over time. This divergence between PVI and IC may be a result of our decision to calculate IC and PVI separately and not use the "connecting formula" ($IC=0.4343 * PVI / ICP$) as described by Marmarou. The divergence could be due to the difference in the formula for calculations of PVI and compliance where PVI is dependent upon the Log to the base 10 of the ratio of P_0 and P_m . Thus, small under-reading of P_m due to, for example air trapped in the injection tubing, will have a more marked effect upon the calculations of PVI than it will on compliance.

There are few reports on outflow resistance in the rat using the bolus injection technique. Bötzel and Brinker have reported values (464 ± 196 mmHg/mL/min) registered in the cisterna magna using this technique (Botel 1994). The present results are quite similar to these even though the experimental setup is different (table 2).

In “conclusion”, the results obtained in paper I showed that it was possible to vary intracranial pressure dynamics in the traumatic brain injury model without causing abnormal increases in baseline ICP. It was also possible to carry out metabolic monitoring with MD. This model can be used to study the effects of secondary insults on the injured brain when ICP is normal but the total intracranial volume is impaired. This situation is common in the clinical setting and it is important to gain a better understanding of the role of intracranial volume buffering upon the pathophysiology of secondary brain injury.

Intracranial volume insults (paper II)

Intraventricular volume injections in combination with reduced intracranial volume (i.e. IC) led to metabolic disturbances in the brain tissue even when ICP was low between the insults. The temporal pattern curves for groups T3V and S3V showed higher increases and slower recovery rates than for the other subgroups in the trauma or sham populations (see figures 11-12 and 13-14, respectively). The patterns for the other groups showed that intracranial volume reduction or intraventricular injections alone were not sufficient to result in metabolic disturbances or membrane degradation. These results support the hypothesis that the brain becomes more vulnerable to secondary insults when IC is reduced, at least for intracranial volume insults.

The secondary brain injury, that follows systemic and intracranial secondary insults, is usually caused by an inadequate oxygen and glucose supply in relation to the metabolic demand. Theoretically, the effect of many of these insults may be further accentuated by disturbances in intracranial dynamics. Even in a patient with normal ICP, decreased IC means a reduced ability to compensate for added intracranial volume. Compared to a patient with normal compliance, a sudden increase of intracranial volume may cause a more pronounced peak elevation of ICP, which may be dangerous even if the ICP elevation is short and transient. It is possible that the results in paper II are explained by this transient ICP elevation and that the increase in energy metabolites probably reflects a disturbed energy metabolism, i.e. transient ischemia, in the area of trauma.

The neurochemical changes shown immediately after the primary injury in paper II correspond well with earlier studies using cortical impact injury models (Nilsson 1990, Bell 1998, Krishnappa 1999). In the earlier studies using the weight drop trauma model (Nilsson 1990, Nilsson 1993), the craniotomy

was left open after injury. The present study was the first to study interstitial biochemical changes after TBI where the craniotomy has been closed. Since our experimental design required bilateral craniotomies, replacement of the bone flaps and insertion of an intraventricular catheter, we were also concerned by the possibility that the surgical manipulation per se would affect our results. The results showed that the effects of surgical manipulation, even with volume reduction, were minimal.

Hypotensive insult (paper III)

In order to mimic clinical conditions in the hypotensive insult study, the insult was induced two hours after trauma when metabolic conditions had recovered (Nilsson 1990, Nilsson 1993). Also a relative moderate and controlled hypotensive insult was used, since this is the most likely hypotensive insult to occur during the NICU period in TBI patients (Winchell 1996). The hypotensive insult in this study caused a small increase in dialysate lactate for all groups with a tendency to remain increased during reperfusion for the trauma injury groups (figure 17). These disturbances were very small. The hypothesis for the study was that hypotension after TBI would have a negative effect on the brains energy-state and that this effect probably would be more accentuated if IC was decreased. The “negative” findings in this study differed both from our study with intraventricular bolus injections as secondary insult (Salci 2006) and from other experimental studies showing that hypotensive insults after TBI accentuate the injury response (see below).

In order to find explanations for the results obtained it is important to compare all studies in more detail. In our previous study using intraventricular injections as a secondary insult, the insult was introduced 20 minutes after the trauma as compared to 120 minutes in the hypotension study. At 20 minutes post-trauma, the tissue is still recovering from the injury while we know that by 120 minutes both metabolic and electrical activity have stabilized (Nilsson 1990, Nilsson 1993). Another probable explanation could be that with slightly reduced IC, a volume insult will create a transient ICP peak that will affect the posttraumatic vulnerable brain whereas hypotension may decrease cerebral blood volume (CBV) and thereby reduce ICP. In the hypotension study ICP did in fact decrease during the hypotensive insults in all groups (see figure 16 and table 5).

Ishige and colleagues (Ishige 1988) showed a significant decrease in ATP values after TBI and hypotensive insult in rats that was not seen with injury or hypotension alone. They used a severe (4-5 atm) fluid percussion injury

(FPI) trauma, a severe hypotensive insult (MABP 30 mmHg, duration 60 min), and started the insult three minutes after impact. Matsushita and colleagues (Matsushita 2001) reported greater regional CBF depression and increased cerebral contusion volume after moderate (2 atm) FPI and hypotensive insult in rats as compared to FPI or insult alone. They used moderate hypotension (60 mmHg) and duration (30 min), similar to our study, but started the insult five minutes after the trauma in contrast to the 2 hours in our study. De Witt and colleagues (DeWitt 1992) showed a significant decrease in CBF, cerebral oxygen delivery and EEG activity after moderate FPI (2.2 atm) followed by mild hemorrhagic hypotension in cats. Injury or hemorrhage alone did not elicit this response. In their study the hemorrhagic insult followed immediately after trauma at a rate of 3 mL/min until approximately 30% of total blood volume was removed, followed by immediate resuscitation. By the end of the hemorrhage the MABP had dropped from approximately 120 to 90 mmHg. Schmoker reported in a porcine model with a cryogenic brain injury that superimposed hypotension caused an early and sustained reduction in cerebral oxygen delivery despite normalization of systemic oxygen delivery (Schmoker 1992). They used moderate hypotension (MABP 50 mmHg for 30 minutes) induced five minutes after the trauma.

It is obvious that the response pattern after TBI and superimposed secondary insults are dependent on the nature and severity of both the trauma and the secondary insult. Furthermore the timing of the secondary insult is certainly also a crucial factor. A possible explanation for the negative results in our study, even though controversial, might be the fact that delayed mild/moderate hypotension after TBI, once the rat is stabilized, may not be as hazardous as has been believed earlier. The results of some other studies where hypotension insult after TBI gave no effect may support that possibility (Lammie 1999, Schutz 2006). It is desirable to explore these questions further regarding the significance of the severity of the secondary insult and time point when the secondary insult occurs for the development of secondary brain injury.

Clinical study (paper IV)

In paper IV the Spiegelberg Compliance Monitor was used in TBI patients to evaluate this monitoring technique and to get an impression of its clinical value. The relation between IC and L/P ratio was analysed and also whether IC influenced the effect of hyperthermia on the L/P ratio. Hyperthermia was chosen as an appropriate secondary insult since it is known to worsen neurological outcome (Dietrich 1992, Kilpatrick 2000), is common in NIC patients

(Kilpatrick 2000) and has a direct effect on ICP (Rossi 2001). The increased ICP by fever is probably partly dependent on the intracranial volume compensatory reserve. Since three out of ten patients included required induced coma treatment, which induces hypothermia, this factor was also included in the analysis.

The results from the statistical model showed significant effect on L/P ratio due to IC, indicating that a lower IC was associated with a higher L/P-ratio (figure 21). This result could be anticipated as a lower IC means reduced intracranial compensatory reserve for added volume and higher risk of ischemia. The coma-treatment group had a higher L/P-ratio compared to the non-coma group (figure 21) despite the fact that thiopental treatment reduces interstitial lactate (Goodman 1996a). The difference might be explained by the fact that the patients in the coma-treatment group were in a “worse” neurological condition, i.e. they had more severe primary brain injury. In the coma treatment group L/P ratio tended to rise when IC decreased and then fall with further decrease in IC. The rise when IC decreased was consistent with our hypothesis but the fall with further decreased IC was more difficult to explain. One possibility is that this might be due to the lactate reducing effects of thiopental coma treatment.

The model for temperature and L/P ratio was significant for the main effect of temperature and the temperature by coma treatment interaction but was not significant for the main effect of coma treatment. For the group without coma treatment the L/P ratio clearly rose as temperature increased to near normal (35°C-36.5°C) and then remained virtually unchanged when temperature rose over 37°C (figure 22). In the coma treatment group the L/P ratio rose when temperature rose above 37° C. However L/P ratio also tended to rise when temperature dropped below 34°C, which is difficult to explain. Low temperatures are probably induced by the barbiturate treatment (Bruder 1998, Roberts 2000), which was required because of the very severe condition of the brain at the time. One possible explanation may thus be that the observed high L/P ratios probably reflect the severe condition of the brain and that effect was stronger than the lactate reducing effect of barbiturates.

The combined model showed that the interaction between IC and temperature was statistically significant (table 7), especially in patients in the coma-treatment group (figure 23). In patients with high temperature L/P ratio increases as IC decreases but in patients who have low temperature there was no effect of IC on L/P ratio. It is possible that patients in the coma-treatment group were in a “poorer neurological condition” (represented by a generally lower IC) which might explain the more pronounced effect on L/P ratio of temperature in these patients. It is important to point out that we were not

able to adequately test the three way interaction among coma treatment, temperature and IC due to the small number of patients. While the differences in figures 23 and 24 are interesting, we can not assert from these results that this was a true difference. A formal test of the difference in the IC by temperature by coma-treatment group will require a larger number of patients.

The results from this study indicate that in TBI patients with high temperatures, the L/P ratio rises when IC decreases, but in patients who have low temperature there is no effect of IC on LP/ ratio. This was especially true in the case of patients with severe TBI requiring induced coma treatment. These data suggest the importance of avoiding hyperthermia in TBI patients, especially in those who have or are expected to develop low IC (monitored or anticipated by their clinical status, CT findings and ICP changes).

CONCLUSIONS

- Intracranial compliance could be decreased in this traumatic brain injury model keeping baseline ICP within normal levels. With this experimental model it was also technically possible to carry out metabolic monitoring with microdialysis. Hence this model can be used to study the role of reduced intracranial compliance in relation to various secondary insults after TBI. (Paper I)
- Decreased intracranial compliance increased the vulnerability of the brain for secondary intracranial volume insults even though ICP was at low level between the insults. (Paper II)
- No synergistic effect was observed on extracellular energy metabolites of late mild posttraumatic hypotension and reduced intracranial compliance after TBI. (Paper III)
- It was possible to monitor IC and MD simultaneously in TBI patients. Higher L/P ratios were seen when intracranial compliance was reduced. IC monitoring in NICU may provide clinically valuable information. (Paper IV)
- There was an indication that in TBI patients with high temperatures L/P ratio rised as IC decreased, especially in patients with severe TBI requiring induced coma treatment. This suggests the importance of avoiding hyperthermia in TBI patients, especially those who have or are expected to develop low intracranial compliance. (Paper IV)

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