Increased intracranial pressure in patients with traumatic brain injury in the intensive care unit

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CHAPTER 1

General introduction and thesis outline

Based on Harary M., Dolmans R.G.F. and Gormley W.B. Intracranial Pressure Monitoring - Review and Avenues for Development.

Sensors (Basel). 2018 Feb 5;18(2):465.

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Traumatic brain injury

Traumatic brain injury (TBI) remains a significant source of morbidity and mortality worldwide[1]. Globally, the annual incidence of TBI is variably estimated at 27 to 69 million[2,3]. In the United States, 2.8 million people sustain a TBI annually with 69.473 TBI-related deaths in 2021[4,5]. In Europe, 2.5 million people suffer from a TBI each year with a mortality rate of 57.000 patients each year[6].

TBI is an injury to the brain caused by an external force disrupting the normal function of the brain[7-10]. Brain injury occurs as a consequence of sudden impact, acceleration-deceleration movements, or a combination of both. At the moment of trauma, blood vessels and brain tissue are stretched, compressed, and torn (primary brain injury)[11]. Secondary brain injury can also occur due to processes initiated by the trauma in the hours to days following the trauma , in particular after moderate to severe brain injury[7,8,11]. This includes a complex set of cellular and biochemical processes (release of inflammatory factors and oxygen free radicals, dysfunction of mitochondria, and excessive release of excitatory neurotransmitters), disruption of the blood-brain barrier[12-14], and loss of cerebral autoregulation. Other important factors are ischemia, cerebral hypoxia, hypotension, cerebral edema, changes in cerebral blood flow (CBF), and increased intracranial pressure (ICP) with and without post-traumatic space occupying lesions. These secondary brain injuries play a major role in permanent brain damage and death resulting from TBI[8,11].

There are two main types of head injuries: penetrating and non-penetrating injuries[7]. Penetrating head injuries (also called open TBI) occurs when an object pierces the skull and enters the brain tissue such as gunshot wounds, bone fragments, or weapons (knives). Non-penetrating head injuries (also called closed head injury or blunt TBI) are caused by an external force that is strong enough to move the brain within the skull such as falls, motor vehicle accidents, strikes to the head, or blast injury[7].

Assessment of TBI

Traumatic brain injury can be classified based on severity into mild, moderate, and severe TBI using the Glasgow Coma Scale (GCS)[15]. The GCS score describes the level of consciousness based on three aspects of responsiveness: eye-opening (E), motor responses (M), and verbal responses (V)[16,17]. The findings of each component of the GCS scale can aggregate into a total GCS between three and 15, three being the worst and 15 being the highest (Table 1). Mild TBI is classified as GCS 13-15, moderate TBI as GCS 9-12 and severe TBI as GCS 3-8[15].

Table 1: Glasgow Coma Scale (GCS) scoring system.

Response	Scale	Score
Eye response	Eyes open spontaneously	4
	Eyes open to verbal command, speech or shout	3
	Eyes open to pain	2
	No eye opening	1
Motor response	Obeys commands for movement	6
	Purposeful movement to painful stimulus	5
	Withdraws in response to pain	4
	Abnormal (spastic) flexion in response to pain	3
	Abnormal (rigid) extension in response to pain	2
	No motor response	1
Verbal	Oriented	5
	Confused conversation, but able to answer questions	4
	Inappropriate words, words discernible	3
	Incomprehensible sounds or speech	2
	No verbal response	1

The severity of TBI can also be assessed by neurological examination focusing on pupil reactivity, focal neurological deficits, lateralizing weakness, and evidence of penetrating or blunt head injury[18]. A pupillary assessment should include the pupillary shape, size, and equality of pupils and reactivity to light[19]. Increased ICP can alter the midbrain function and cause abnormalities in pupil reactivity, size, and symmetry[20]. Pupil reactivity has both diagnostic as well as prognostic value[20,21]. Pupillary abnormalities are associated with worse outcome[20,22]. Bilaterally fixed pupils in patients with TBI have a poor outcome in 70-90% of cases (vegetative state or dead) compared to around 30% with bilaterally reactive pupils[18].

Besides physical examination, the extent of head injury with the associated intracranial pathologic conditions can also be assessed in the acute setting by neuro-imaging techniques such as head computed tomography (head-CT)[23]. Imaging findings that can be found in patients with TBI are skull fractures, epidural hematomas, subdural hematomas, subarachnoid hemorrhages, intraventricular hemorrhages, brain contusions, diffuse axonal injury, diffuse cerebral edema, herniation and vascular injuries. CT imaging findings are essential in guiding the management of TBI[23].

Intracranial pressure

The systematic discussion of ICP and its determinants dates back to the work of Scottish anatomist Alexander Monro and a compatriot surgeon, George Kellie, at the turn of the 18th century. Their model for ICP, the Monro–Kellie doctrine, which was later refined by American neurosurgeon, Harvey Cushing, details the basic principles that govern ICP[24-26]. Principally, the volume of the intracranial cavity is constant under normal conditions, and, therefore, the maintenance of a steady ICP depends on the volume of its contents. The intracranial contents include (1) brain tissue; (2) blood; and (3) cerebrospinal fluid (CSF) (Figure 1)[27-29]. As brain tissue is easily damaged by small pressure, steady ICP requires balancing the in- and outflow of the fluid components; namely, there must be a balance between the inflow of arterial blood and the outflow of venous blood from the head, as well as between the rate of CSF production and drainage. Elevated ICP can therefore result from any mechanism that increases the volume of any of the three components. Alternatively, ICP can also increase by the addition of a fourth component, such as a mass, intracranial hemorrhage or cerebral edema that expands beyond the ability of the system to compensate by decreasing the volume of another.

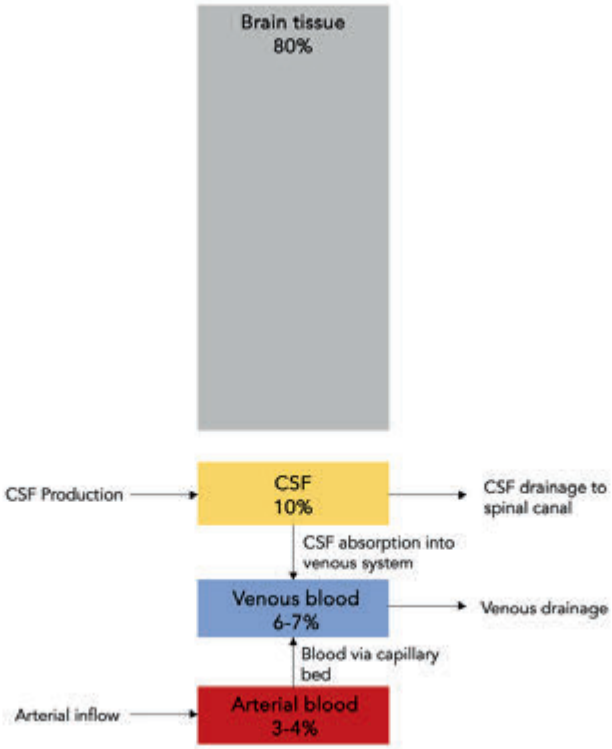

Figure 1: The Monro–Kellie model for the contents of the intracranial compartment. 'Brain tissue' includes neurons, glia, extracellular fluid and cerebral microvasculature. 'Venous' and 'Arterial blood' represents the intracranial blood volume in macro-vasculature and cerebral venous sinuses. 'CSF' includes ventricular and cisternal CSF.

Some changes in mean ICP are expected under regular physiologic conditions, including changes in posture, brain activity, cardiovascular function, respiratory function and adrenergic tone[30-33]. Since some variability in ICP is expected, clinical use of ICP monitoring uses a time-averaged ICP to establish baseline, with overnight measurement over at least 30 minutes considered to be the 'gold standard' in non-comatose patients[34]. Similarly, alterations in ICP reach clinical significance when they are sustained longer than at least 5 min. Physiologic boundaries of mean ICP are 7–15 mm Hg in supine adults, 3–7 mm Hg in children and 1.5–6 mm Hg in infants, though mean ICP in pediatric populations may vary depending on age and are not as well established[35]. The maintenance of ICP within its physiologic boundaries is of critical importance to prevent brain injury[36-38]. Elevated ICP-related injury occurs primarily via one of two mechanisms: (1) cerebral ischemia and (2) brain(stem) herniation. Cerebral blood flow is tightly linked to

cerebral perfusion pressure (CPP), which is governed by both mean arterial pressure (MAP) and ICP through the following relationship, CPP = MAP-ICP. Accordingly, as ICP increases, MAP is increased, primarily through a rise in cardiac output, in order to maintain a steady CPP. In the presence of elevated ICP beyond the ability for compensation through elevation of MAP, CPP will be compromised, and cerebral ischemia may follow. While under the Monro–Kellie doctrine, the intracranial space is a constant, enclosed space, the brain and intracranial CSF continue, of course, through the foramen magnum at the base of the skull to become the brainstem, spinal cord, and the CSF-filled spinal canal within its dural space. When ICP is sufficiently elevated, the pressure differential between the intracranial cavity and the spinal canal can cause the downward motion of brain tissue (i.e., herniation), which can compress vital brainstem and neurovascular structures, and subsequently lead to severe neurological outcomes including death[38-40].

As some variability in ICP is expected even under physiologic conditions, there are intrinsic compensatory mechanisms to maintain a stable mean ICP. Foremost among these is that ability to modify the brain venous blood pool. Additionally, there is an ability, albeit limited, of some CSF to expand further out of the intracranial space and into the spinal canal[41]. This compensatory reserve is finite and is dependent on the compliance of the system. When the reserve is depleted, small elevations in volume will lead to potentially dangerous sustained elevations in ICP (Figure 2). Alongside these mechanisms to attenuate changes in ICP, cerebrovascular autoregulation functions to maintain the necessary CPP in the face of ICP changes by way of altering cerebral arteriolar resistance. Autoregulation, however, is only effective between a CPP of 50–150 mmHg, below and above which hypoperfusion and cerebral edema may ensue, respectively (Figure 3). In addition, autoregulatory capacity is also dependent on arterial pressure of carbon dioxide ($PaCO_2$). Hypercapnia causes dilation of the cerebral vessels leading to an increase in CBF and a risk of hyperperfusion. Conversely, longstanding hypocapnia causes vasoconstriction, which may result in ischemia[42,43].

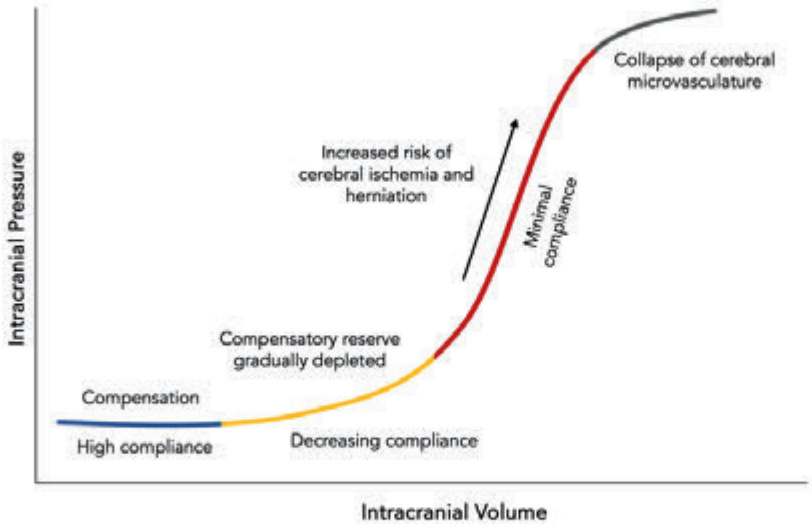

Figure 2: Pressure–volume curve for ICP. The pressure–volume curve has four 'zones': (1) baseline intracranial volume with good compensatory reserve and high compliance (blue); (2) gradual depletion of compensatory reserve as intracranial volume increases (yellow); (3) poor compensatory reserve and increased risk of cerebral ischemia and herniation (red); and (4) critically high ICP causing collapse of cerebral microvasculature and disturbed cerebrovascular reactivity (grey).

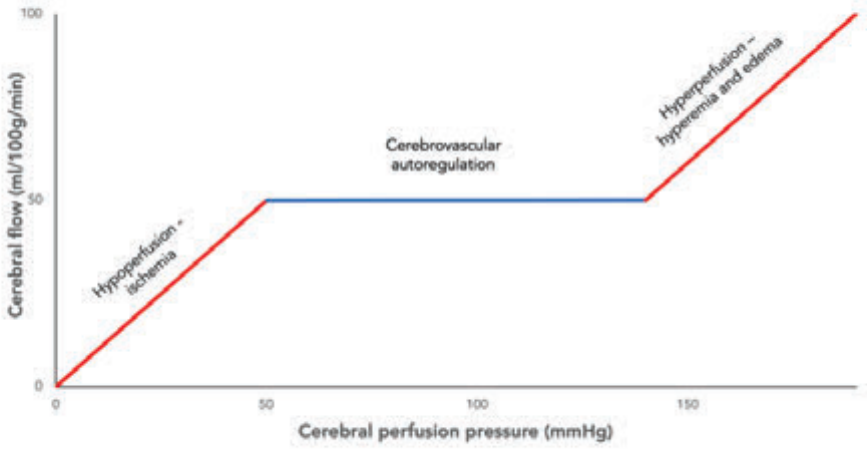

Figure 3: Cerebral autoregulation capacity.

Measurement of intracranial pressure

The early characterization of the components of ICP and its importance for clinical outcomes led to a desire to measure ICP for the purpose of guiding clinical management. The earliest surgical approach to reduce ICP was through the use of the external ventricular drain (EVD), which was used to drain CSF in pediatric patients with congenital hydrocephalus[44]. It was only around the turn of the 20th century that EVDs could be placed safely, and with aseptic technique to avoid iatrogenic intracranial infections[45]. Soon thereafter, the first instance of ICP monitoring using an EVD-based manometric system was described by Adson and Lillie in their landmark 1927 paper[46]. Since that time, the indication for ICP monitoring has expanded, and, currently, the most common neurological and neurosurgical pathologies that require ICP monitoring include TBI, subarachnoid hemorrhage (SAH), and hydrocephalus.

Methods for ICP monitoring can be divided into invasive and non-invasive approaches. Invasive methods include fluid-based systems and implantable micro-transducers. Non-invasive methods, most of which offer indirect measurement of ICP, are outside the scope of this thesis and will not be discussed here.

Of the invasive methods, ICP monitoring using an EVD is considered as the gold standard, not only for its accuracy but also because it additionally serves a therapeutic purpose by allowing CSF drainage[34,47]. EVDs allow for fluid-based monitoring as the pressure in the catheter equilibrates with the intraventricular pressure. This pressure transmits into an external saline-filled tube through a stain-gauge transducer from which the pressure measurement is made. The insertion of an EVD may be difficult in patients with inherently small ventricles size or those with ventricular compression attributable to advanced brain swelling[34,47]. Additionally, there is a 5–7% risk of hemorrhage during insertion[48,49], causing extra damage to a possible healthy part of brain tissue. EVDs are not suitable for long-term ICP monitoring since risk of intracranial infection starts to increase with an estimated overall risk of 5% after five days[34]. Another fluid-based system is the subarachnoid screw, which is inserted through a hole drilled in the skull whose tip projects through the dura into the subarachnoid space[50,51]. These devices, however, cannot drain CSF and have a considerable risk of local wound infection[52].

ICP can also be measured using implantable microtransducers such as strain gauge devices, pneumatic sensors and fiber-optic sensors (technical review by Zhang et

al.[53]). In strain gauge devices, ICP changes cause the diaphragm to bend, leading to changes in the electrical resistance that are used to calculate ICP[54]. Pneumatic sensors have a balloon in the distal end of the probe, where pressure exerted on the balloon is equal to the pressure of the surrounding tissue (i.e., ICP). Pneumatic sensors have also been used to measure intracranial compliance[54]. In fiber-optic sensors, changes in ICP move a displaceable mirror at the tip of the sensor, altering the intensity of the light reflected back along the fiber optic cable[50,54]. Most micro-transducers probes tips are placed intraparenchymally, but these can also be placed in the intraventricular, subarachnoid, subdural or epidural compartment (Figure 4). Advantages of implantable microtransducers are lower infection rates and risks of hemorrhage compared to EVDs[34]. However, these are more expensive and, with the exception of pneumatic sensors, generally cannot be recalibrated once in situ, which can affect the precision of ICP measurements[47,52,54]. Generally, micro-transducers are used in situations where EVD placement is not successful, when clinicians judge that CSF drainage is not likely to be necessary or due to regional variation in treatment algorithms per trauma center, where CSF drainage is not the standard of care in elevated ICP.

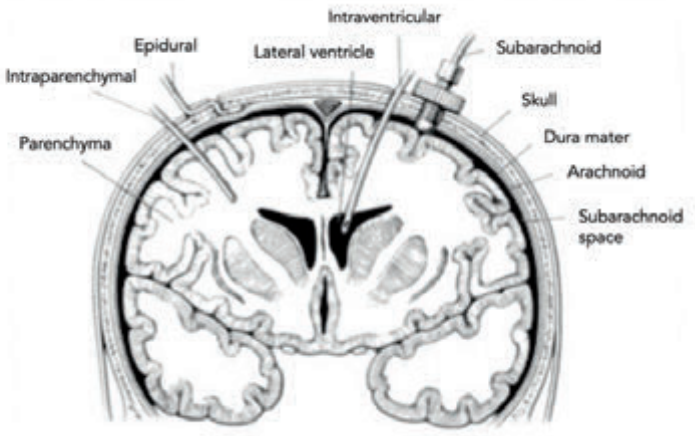

Figure 4: Sites for invasive ICP monitoring. These sites represent actual and potential spaces in the intracranial cavity in which ICP can be measured. Intraventricular monitoring with EVDs is the most commonly accessed site in clinical practice, followed by intraparenchymal probes. Reproduced with permission[55].

While the management of ICP is of clear clinical benefit, there is no consensus in the literature about whether ICP monitoring provides clinical benefit as compared to management based solely on the patient's neurological exam, imaging findings and clinicians' acumen. While some studies demonstrate that ICP monitoring is associated with improved survival[56-64], others suggest that ICP monitoring is not only not beneficial, but may, in fact, lead to worse outcomes[65-71]. Specifically, in some studies, ICP monitoring was associated with a significant increase in mortality, longer hospital length of stay, complication rate and increased utilization of hospital resources, compared to patients managed without ICP monitoring[65-70]. The only randomized controlled trial of ICP monitoring in patients with TBI was conducted by Chesnut et al. in 2012[71]. The authors compared outcomes between patients whose treatment was guided by imaging and clinical exam alone, and those who additionally received invasive ICP monitoring. The overall 6-month mortality rate was approximately 40%, with no survival benefit seen in patients who received ICP monitoring compared to those in whom treatment was guided only by neurologic examination and serial CT imaging. Serious criticism has been discussed in the Neurotraumatology research community as the population of TBI was randomized in a country outside the high- and middle-income countries with high-end ICU care. The country of this RCT had less resources, increased pre-hospital times and a different ICU care compared to the USA and most countries of Europe. Although this RCT has been performed with scientific robust analysis, the results and conclusions cannot

be generalized to the neurocritical care of hospitals in high income countries. On the other hand, these conclusions are very valid as most of neurotrauma occurs in LMIC's (WHO Ref) with less resources and other ways of treating the severe TBI patients.

Taking these in sum, there remains room for improvement of the clinical utility of ICP monitoring in critically ill patients.

Management of intracranial pressure

For the management of ICP, a three-tiered approach is developed that utilizes various treatments to target different mechanisms[72,73]. Higher tiers reflect more intensive management. Failure to control ICP within one tier should prompt rapid progression to the next tier treatment (Figure 5).

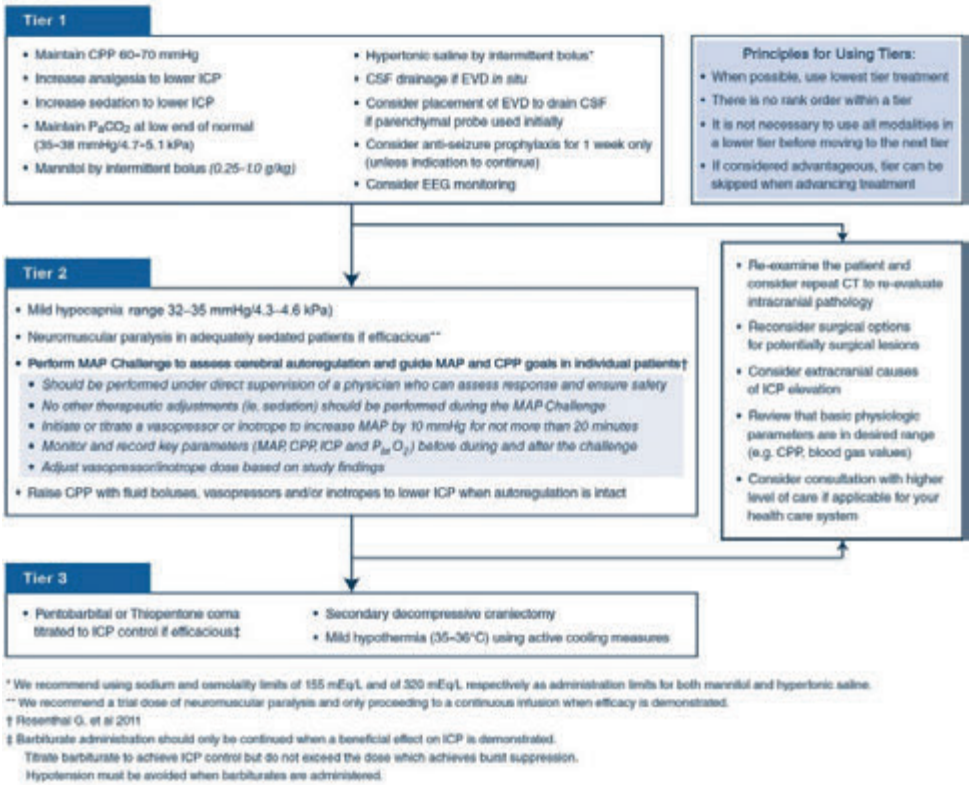

Figure 5: Three-tiered approach for the management of intracranial pressure in TBI patients in the ICU. Image from: Hawryluk et al[72].
CCP: cerebral perfusion pressure; ICP: intracranial pressure; CSF: cerebrospinal fluid; EVD: external ventricular drain; PaCO2: arterial partial pressure of carbon dioxide; EEG: electro-encephalogram; MAP: mean arterial pressure; CT: computed tomography.

There are many different treatment options for the management of increased ICP in TBI patients in the intensive care unit (ICU). They include, but are not limited to, analgesics and sedatives, CSF drainage, hyperosmolar therapy, decompressive craniectomy, prophylactic hypothermia, ventilation therapies, and seizure prophylaxis[39,72,73]. The current thesis will only focus on analgesics and sedatives since that is one of the first steps in the management of TBI patients in the ICU and sufficient evidence and guidelines for this specific treatment are still lacking.

Analgesics and sedatives

Analgesics and sedatives have several cerebral protective effects in patients with TBI such as reducing cerebral blood flow and reducing the cerebral metabolic rate of oxygen consumption (CMRO2) thereby improving the cerebral tolerance to ischemia and limiting the demand and supply mismatch in conditions of impaired autoregulation[74-76]. In addition, sedative agents reduce pain and agitation and improve the tolerance of an endotracheal tube leading to a decrease in sympathetic activity with a reduction of mean arterial blood pressure preventing increased ICP[74,75]. There are various sedative agents that are used in the treatment of TBI patients, such as propofol, benzodiazepines, opioids, dexmedetomidine, barbiturates and ketamine[76]. Table 1 shows the mechanism of action, physiologic cerebral effects, advantages and disadvantages and adverse effects of each sedative agent in patients with TBI.

Table 2: Sedative agents and their mechanisms of action, cerebral physiologic effects, advantages and disadvantages and adverse effects.

Sedative agent	Mechanism of action	Cerebral physiologic effect	Advantages	Disadvantages	Adverse effects
Propofol	GABA-R agonist	↓ ICP ↓ CBF ↓ $CMRO_2$ Preserved CO_2 reactivity and cerebral autoregulation ↓ Cerebral electrical activity, can be used to induce EEG burst suppression (at high dose)	Clearance independent of renal or hepatic function. Rapid onset and fast recovery.	No analgesic effect Tolerance and tachyphylaxis ↑ Triglycerides ↑ Caloric intake	Hypotension Propofol infusion syndrome
Midazolam	GABA-R agonist	Slight ↓ ICP ↓ CBF ↓ $CMRO_2$ Preserved CO_2 reactivity and cerebral autoregulation Anti-epileptic effect	Amnesia Rapid onset Less haemodynamic instability than propofol (may prevent CPP reductions)	Tolerance and tachyphylaxis Accumulates in renal dysfunction Active metabolites	Delirium Apnea
Morphine	μ-receptor agonist	Limited effect on ICP and CBF ↓ MAP/CPP transiently following bolus	Analgesia Less peripheric accumulation than fentanyl	Hypotension Accumulation with hepatic/renal impairment	Apnea Pruritus Nausea

Sedative agent	Mechanism of action	Cerebral physiologic effect	Advantages	Disadvantages	Adverse effects
Fentanyl, sufentanil	μ-receptor agonists	Limited effect on ICP and CBF ↓ MAP/CPP transiently following bolus	More potent opioid than morphine (sufentanil is 1000× more potent than morphine)	Accumulation with hepatic impairment	Apnea Pruritus Muscle rigidity
Remifentanil	μ-receptor agonist	No changes in ICP or CBF during drug infusion	500× more potent than morphine Rapid onset and fast recovery to permit neurological assessment Clearance independent of renal or hepatic function	Tachyphylaxis Higher cost than other opiates	Hyperalgesia at the cessation of drug infusion
Dexmede-tomidine	α_2-agonist	Limited effect on ICP	Sedative, analgesic and anxiolytic Short acting, no accumulation, patient may be frequently assessed neurologically Minimal respiratory depression Reduces delirium	Limited experience in patients with TBI	Arrhythmias Hypotension Bradycardia

Sedative agent	Mechanism of action	Cerebral physiologic effect	Advantages	Disadvantages	Adverse effects
Barbiturates	GABA-R agonist	↓↓ ICP ↓↓ CBF that is proportional to the ↓↓ $CMRO_2$ ↓↓ MAP	Second-line treatment of refractory ICP	Adrenal dysfunction	Immune suppression Hypotension
Ketamine	NMDA-R antagonist	Limited effect on ICP Minimal decrease in CBF and $CMRO_2$	Short acting, rapid onset Induces sedation, analgesia and anaesthesia No respiratory depression Haemodynamic stability, preserves MAP	Increases secretions	Hallucinations
Inhaled anaesthetics	Not fully established: may act at several sites	Dose-dependent effects on CBF: ↓ CBF at low concentrations, ↑ CBF at high concentrations ICP may increase after increase in CBF ↓ Cerebral electrical activity, ↓ $CMRO_2$	Rapid elimination ↑ CBF in patients with cerebral ischaemia	↑ ICP due to ↑ CBF Data very preliminary	Malignant hyperthermia

ICP: intracranial pressure; CBF: cerebral blood flow; CMRO: cerebral metabolic rate of oxygen; EEG: electroencephalogram; CPP: cerebral perfusion pressure; MAP: mean arterial pressure; TBI: traumatic brain injury[74,75].

According to the current Brain Trauma Foundation Guidelines, there is a lack of high-quality evidence to recommend one sedative agent over another, except for high-dose barbiturate administration which is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment[39].

Aim and outline of this thesis

The first part of this thesis will focus on the measurement of intracranial pressure (ICP). Increased ICP after traumatic brain injury (TBI) is an important factor of secondary brain injury and monitoring ICP is one of the cornerstones in the treatment of TBI patients in the intensive care unit (ICU). The two most commonly used invasive methods to measure ICP are external ventricular drains (EVDs) and intraparenchymal monitors (IPMs). These two methods of ICP monitoring are compared in **chapter 2**. We aimed to investigate factors associated with receiving either ICP monitor type and to compare TBI patients monitored with an EVD versus an IPM in relation to clinical management, mortality, and functional outcome.

Information from ICP waveforms, besides the data collected during routine ICU care of TBI patients such as lab values, vital signs and EEG monitoring, form – when aggregated – enormous amounts of data about the individual patient, also called "big data". With the use of artificial intelligence, these enormous amounts of data can be analyzed. In **chapter 3** we discuss how "big data" and artificial intelligence can play an important role in the management of patients with TBI in the ICU and how we can prepare for this change in healthcare. As an example of how artificial intelligence and big data can be employed in ICU care of the TBI patient, we sought to develop a machine learning (ML) model differentiating intracranial pressure (ICP) waveforms originating from an external ventricular drain (EVD) or intraparenchymal ICP monitor (IPM) (**chapter 4**).

The second part of this thesis will focus on the management of increased ICP in TBI patients in the ICU using analgo-sedation. Because of limited evidence and guidelines for the use of analgesics and sedatives in TBI patients in the ICU, we hypothesized that significant practice-pattern variation may exist in the use of analgo-sedation across patients and institutions. **Chapter 5** describes the results of an international survey quantifying practice-pattern variation in analgosedative management of TBI patients requiring ICU management.

To further analyze the analgo-sedative management of TBI patients, a retrospective analysis was performed to quantify the different sedation intensities administered in moderate to severe TBI (msTBI) patients from seven US level-1 trauma centers enrolled within the prospective Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) cohort study (**chapter 6**). In addition, we aimed to investigate the effect of midazolam-based sedation vs. non-midazolam-based sedation on the need for ICP rescue therapies and clinical outcome in sTBI patients from 14 ICUs in Europe and Australia (**chapter 7**).

Although the care of TBI patients in the ICU is improving with improved treatment options and technological opportunities, it is important to also pay attention to the wishes and needs of the patient and their families. Therefore, the final part of this thesis (**chapter 8**) will focus on the implementation of a palliative care approach in TBI patients in the ICU.

Chapter 9 contains a summary, and **chapter 10** concludes the thesis with a general discussion about the current status of intracranial pressure management in TBI patients in the ICU and discusses future perspectives.

References

1. Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC. The impact of traumatic brain injuries: a global perspective. NeuroRehabilitation 2007;22(5):341-53. (In eng).
2. GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18(1):56-87. (In eng). DOI: 10.1016/s1474-4422(18)30415-0.
3. Dewan MC, Rattani A, Gupta S, et al. Estimating the global incidence of traumatic brain injury. J Neurosurg 2018:1-18. (In eng). DOI: 10.3171/2017.10.Jns17352.
4. Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic Brain Injury-Related Emergency Department Visits, Hospitalizations, and Deaths - United States, 2007 and 2013. MMWR Surveill Summ 2017;66(9):1-16. (In eng). DOI: 10.15585/mmwr.ss6609a1.
5. Centers for Disease Control and Prevention (CDC). Traumatic Brain Injury and Concussion. (https://www.cdc.gov/traumatic-brain-injury/data-research/?CDC_AAref_Val=https://www.cdc.gov/traumaticbraininjury/data/index.html).
6. CENTER-TBI. Traumatic Brain Injury: Fact sheets and policy brief.
7. National Institute of Neurological Disorders and Stroke. Traumatic brain injury (TBI). (https://www.ninds.nih.gov/health-information/disorders/traumatic-brain-injury-tbi).
8. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Lancet Neurol 2008;7(8):728-41. (In eng). DOI: 10.1016/s1474-4422(08)70164-9.
9. Centers for Disease Control and Prevention (CDC). Traumatic Brain Injury & Concussion: Moderate and severe TBI. (https://www.cdc.gov/traumaticbraininjury/moderate-severe/index.html).
10. Menon DK, Schwab K, Wright DW, Maas AI. Position statement: definition of traumatic brain injury. Arch Phys Med Rehabil 2010;91(11):1637-40. (In eng). DOI: 10.1016/j.apmr.2010.05.017.
11. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. Br J Anaesth 2007;99(1):4-9. (In eng). DOI: 10.1093/bja/aem131.
12. Verweij BH, Muizelaar JP, Vinas FC, Peterson PL, Xiong Y, Lee CP. Impaired cerebral mitochondrial function after traumatic brain injury in humans. J Neurosurg 2000;93(5):815-20. (In eng). DOI: 10.3171/jns.2000.93.5.0815.
13. Hakiminia B, Alikiaii B, Khorvash F, Mousavi S. Oxidative stress and mitochondrial dysfunction following traumatic brain injury: From mechanistic view to targeted therapeutic opportunities. Fundam Clin Pharmacol 2022;36(4):612-662. (In eng). DOI: 10.1111/fcp.12767.

14. Gennarelli GA, Graham DI. Neuropathology. In: Textbook Of Traumatic Brain Injury. Washington, DC: American Psychiatric Association. 2005: pp. 27–33.
15. Saatman KE, Duhaime AC, Bullock R, Maas AI, Valadka A, Manley GT. Classification of traumatic brain injury for targeted therapies. J Neurotrauma 2008;25(7):719-38. (In eng). DOI: 10.1089/neu.2008.0586.
16. Jain S, Iverson LM. Glasgow Coma Scale. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.
17. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;2(7872):81-4. (In eng). DOI: 10.1016/s0140-6736(74)91639-0.
18. Moppett IK. Traumatic brain injury: assessment, resuscitation and early management. Br J Anaesth 2007;99(1):18-31. (In eng). DOI: 10.1093/bja/aem128.
19. Adoni A, McNett M. The pupillary response in traumatic brain injury: a guide for trauma nurses. J Trauma Nurs 2007;14(4):191-6; quiz 197-8. (In eng). DOI: 10.1097/01.jtn.0000318921.90627.fe.
20. Oddo M, Taccone F, Galimberti S, Rebora P, Citerio G. Outcome Prognostication of Acute Brain Injury using the Neurological Pupil Index (ORANGE) study: protocol for a prospective, observational, multicentre, international cohort study. BMJ Open 2021;11(5):e046948. (In eng). DOI: 10.1136/bmjopen-2020-046948.
21. Sharshar T, Citerio G, Andrews PJ, et al. Neurological examination of critically ill patients: a pragmatic approach. Report of an ESICM expert panel. Intensive Care Med 2014;40(4):484-95. (In eng). DOI: 10.1007/s00134-014-3214-y.
22. Volpi PC, Robba C, Rota M, Vargiolu A, Citerio G. Trajectories of early secondary insults correlate to outcomes of traumatic brain injury: results from a large, single centre, observational study. BMC Emerg Med 2018;18(1):52. (In eng). DOI: 10.1186/s12873-018-0197-y.
23. Schweitzer AD, Niogi SN, Whitlow CT, Tsiouris AJ. Traumatic Brain Injury: Imaging Patterns and Complications. Radiographics 2019;39(6):1571-1595. (In eng). DOI: 10.1148/rg.2019190076.
24. Monro A. Observations on the Structure and Functions of the Nervous System: Creech and Johnson, Edinburgh, UK, 1783.
25. Kellie G. Appearances observed in the dissection of two individuals; death from cold and congestion of the brain. Trans Med-Chir Soc Edinburgh 1824, 1, 84.
26. Cushing H. The Third Circulation in Studies in Intracranial Physiology and Surgery: Oxford University Press: London, UK, 1926.
27. Greenberg M, (Ed.). Neuromonitoring. Handbook of Neurosurgery, 8th ed.: Thieme: New York, NY, USA, 2016; pp. 856–881.
28. Leffert LR, Schwamm LH. Neuraxial anesthesia in parturients with intracranial pathology: a comprehensive review and reassessment of risk. Anesthesiology 2013;119(3):703-18. (In eng). DOI: 10.1097/ALN.0b013e31829374c2.

29. Morton R, Ellenbogen R. Intracranial hypertension. Principles of Neurological Surgery, 3rd ed.: Saunders/Elsevier: Philadelphia, PA, USA, 2012; pp. 311–323.
30. Donnelly J, Budohoski KP, Smielewski P, Czosnyka M. Regulation of the cerebral circulation: bedside assessment and clinical implications. Crit Care 2016;20(1):129. (In eng). DOI: 10.1186/s13054-016-1293-6.
31. Cavus E, Bein B, Dörges V, et al. Brain tissue oxygen pressure and cerebral metabolism in an animal model of cardiac arrest and cardiopulmonary resuscitation. Resuscitation 2006;71(1):97-106. (In eng). DOI: 10.1016/j.resuscitation.2006.03.007.
32. Bowton DL, Bertels NH, Prough DS, Stump DA. Cerebral blood flow is reduced in patients with sepsis syndrome. Crit Care Med 1989;17(5):399-403. (In eng). DOI: 10.1097/00003246-198905000-00004.
33. Lundberg N. Continuous recording and control of ventricular fluid pressure in neurosurgical practice. Acta Psychiatr Scand Suppl 1960;36(149):1-193. (In eng).
34. Czosnyka M, Pickard JD. Monitoring and interpretation of intracranial pressure. J Neurol Neurosurg Psychiatry 2004;75(6):813-21. (In eng). DOI: 10.1136/jnnp.2003.033126.
35. Kukreti V, Mohseni-Bod H, Drake J. Management of raised intracranial pressure in children with traumatic brain injury. J Pediatr Neurosci 2014;9(3):207-15. (In eng). DOI: 10.4103/1817-1745.147572.
36. Gilland O. Normal cerebrospinal-fluid pressure. N Engl J Med 1969;280(16):904-5. (In eng).
37. Gilland O, Tourtellotte WW, O'Tauma L, Henderson WG. Normal cerebrospinal fluid pressure. J Neurosurg 1974;40(5):587-93. (In eng). DOI: 10.3171/jns.1974.40.5.0587.
38. Smith M. Monitoring intracranial pressure in traumatic brain injury. Anesth Analg 2008;106(1):240-8. (In eng). DOI: 10.1213/01.ane.0000297296.52006.8e.
39. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery 2017;80(1):6-15. (In eng). DOI: 10.1227/neu.0000000000001432.
40. Treggiari MM, Schutz N, Yanez ND, Romand JA. Role of intracranial pressure values and patterns in predicting outcome in traumatic brain injury: a systematic review. Neurocrit Care 2007;6(2):104-12. (In eng). DOI: 10.1007/s12028-007-0012-1.
41. Czosnyka M, Citerio G. Brain compliance: the old story with a new 'et cetera'. Intensive Care Med 2012;38(6):925-7. (In eng). DOI: 10.1007/s00134-012-2572-6.
42. Meng L, Gelb AW. Regulation of cerebral autoregulation by carbon dioxide. Anesthesiology 2015;122(1):196-205. (In eng). DOI: 10.1097/aln.0000000000000506.

43. Kinoshita K. Traumatic brain injury: pathophysiology for neurocritical care. J Intensive Care 2016;4:29. (In eng). DOI: 10.1186/s40560-016-0138-3.
44. Srinivasan VM, O'Neill BR, Jho D, Whiting DM, Oh MY. The history of external ventricular drainage. J Neurosurg 2014;120(1):228-36. (In eng). DOI: 10.3171/2013.6.Jns121577.
45. Aschoff A, Kremer P, Hashemi B, Kunze S. The scientific history of hydrocephalus and its treatment. Neurosurg Rev 1999;22(2-3):67-93; discussion 94-5. (In eng). DOI: 10.1007/s101430050035.
46. Adson AW, Lillie WI. The relationship of intracranial pressure, choked disc, and intraocular tension. Trans Am Acad Opthalmol 1927, 138–145.
47. Padayachy LC, Figaji AA, Bullock MR. Intracranial pressure monitoring for traumatic brain injury in the modern era. Childs Nerv Syst 2010;26(4):441-52. (In eng). DOI: 10.1007/s00381-009-1034-0.
48. Binz DD, Toussaint LG, 3rd, Friedman JA. Hemorrhagic complications of ventriculostomy placement: a meta-analysis. Neurocrit Care 2009;10(2):253-6. (In eng). DOI: 10.1007/s12028-009-9193-0.
49. Bauer DF, Razdan SN, Bartolucci AA, Markert JM. Meta-analysis of hemorrhagic complications from ventriculostomy placement by neurosurgeons. Neurosurgery 2011;69(2):255-60. (In eng). DOI: 10.1227/NEU.0b013e31821a45ba.
50. Kawoos U, McCarron RM, Auker CR, Chavko M. Advances in Intracranial Pressure Monitoring and Its Significance in Managing Traumatic Brain Injury. Int J Mol Sci 2015;16(12):28979-97. (In eng). DOI: 10.3390/ijms161226146.
51. Vries JK, Becker DP, Young HF. A subarachnoid screw for monitoring intracranial pressure. Technical note. J Neurosurg 1973;39(3):416-9. (In eng). DOI: 10.3171/jns.1973.39.3.0416.
52. Bekar A, Doğan S, Abaş F, et al. Risk factors and complications of intracranial pressure monitoring with a fiberoptic device. J Clin Neurosci 2009;16(2):236-40. (In eng). DOI: 10.1016/j.jocn.2008.02.008.
53. Zhang X, Medow JE, Iskandar BJ, et al. Invasive and noninvasive means of measuring intracranial pressure: a review. Physiol Meas 2017;38(8):R143-r182. (In eng). DOI: 10.1088/1361-6579/aa7256.
54. Raboel PH, Bartek J, Jr., Andresen M, Bellander BM, Romner B. Intracranial Pressure Monitoring: Invasive versus Non-Invasive Methods-A Review. Crit Care Res Pract 2012;2012:950393. (In eng). DOI: 10.1155/2012/950393.
55. Lyons MK, Meyer FB. Cerebrospinal fluid physiology and the management of increased intracranial pressure. Mayo Clin Proc 1990;65(5):684-707. (In eng). DOI: 10.1016/s0025-6196(12)65131-3.
56. Gerber LM, Chiu YL, Carney N, Härtl R, Ghajar J. Marked reduction in mortality in patients with severe traumatic brain injury. J Neurosurg 2013;119(6):1583-90. (In eng). DOI: 10.3171/2013.8.Jns13276.

57. Alali AS, Fowler RA, Mainprize TG, et al. Intracranial pressure monitoring in severe traumatic brain injury: results from the American College of Surgeons Trauma Quality Improvement Program. J Neurotrauma 2013;30(20):1737-46. (In eng). DOI: 10.1089/neu.2012.2802.
58. Stein SC, Georgoff P, Meghan S, Mirza KL, El Falaky OM. Relationship of aggressive monitoring and treatment to improved outcomes in severe traumatic brain injury. J Neurosurg 2010;112(5):1105-12. (In eng). DOI: 10.3171/2009.8.Jns09738.
59. Farahvar A, Gerber LM, Chiu YL, Carney N, Härtl R, Ghajar J. Increased mortality in patients with severe traumatic brain injury treated without intracranial pressure monitoring. J Neurosurg 2012;117(4):729-34. (In eng). DOI: 10.3171/2012.7.Jns111816.
60. Dawes AJ, Sacks GD, Cryer HG, et al. Intracranial pressure monitoring and inpatient mortality in severe traumatic brain injury: A propensity score-matched analysis. J Trauma Acute Care Surg 2015;78(3):492-501; discussion 501-2. (In eng). DOI: 10.1097/ta.0000000000000559.
61. You W, Feng J, Tang Q, et al. Intraventricular intracranial pressure monitoring improves the outcome of older adults with severe traumatic brain injury: an observational, prospective study. BMC Anesthesiol 2016;16(1):35. (In eng). DOI: 10.1186/s12871-016-0199-9.
62. Shen L, Wang Z, Su Z, et al. Effects of Intracranial Pressure Monitoring on Mortality in Patients with Severe Traumatic Brain Injury: A Meta-Analysis. PLoS One 2016;11(12):e0168901. (In eng). DOI: 10.1371/journal.pone.0168901.
63. Talving P, Karamanos E, Teixeira PG, et al. Intracranial pressure monitoring in severe head injury: compliance with Brain Trauma Foundation guidelines and effect on outcomes: a prospective study. J Neurosurg 2013;119(5):1248-54. (In eng). DOI: 10.3171/2013.7.Jns122255.
64. Lane PL, Skoretz TG, Doig G, Girotti MJ. Intracranial pressure monitoring and outcomes after traumatic brain injury. Can J Surg 2000;43(6):442-8. (In eng).
65. Tang A, Pandit V, Fennell V, et al. Intracranial pressure monitor in patients with traumatic brain injury. J Surg Res 2015;194(2):565-570. (In eng). DOI: 10.1016/j.jss.2014.11.017.
66. Aiolfi A, Benjamin E, Khor D, Inaba K, Lam L, Demetriades D. Brain Trauma Foundation Guidelines for Intracranial Pressure Monitoring: Compliance and Effect on Outcome. World J Surg 2017;41(6):1543-1549. (In eng). DOI: 10.1007/s00268-017-3898-6.
67. Piccinini A, Lewis M, Benjamin E, Aiolfi A, Inaba K, Demetriades D. Intracranial pressure monitoring in severe traumatic brain injuries: a closer look at level 1 trauma centers in the United States. Injury 2017;48(9):1944-1950. (In eng). DOI: 10.1016/j.injury.2017.04.033.

68. Haddad S, Aldawood AS, Alferayan A, Russell NA, Tamim HM, Arabi YM. Relationship between intracranial pressure monitoring and outcomes in severe traumatic brain injury patients. Anaesth Intensive Care 2011;39(6):1043-50. (In eng). DOI: 10.1177/0310057x1103900610.
69. Shafi S, Diaz-Arrastia R, Madden C, Gentilello L. Intracranial pressure monitoring in brain-injured patients is associated with worsening of survival. J Trauma 2008;64(2):335-40. (In eng). DOI: 10.1097/TA.0b013e31815dd017.
70. Cremer OL, van Dijk GW, van Wensen E, et al. Effect of intracranial pressure monitoring and targeted intensive care on functional outcome after severe head injury. Crit Care Med 2005;33(10):2207-13. (In eng). DOI: 10.1097/01.ccm.0000181300.99078.b5.
71. Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. N Engl J Med 2012;367(26):2471-81. (In eng). DOI: 10.1056/NEJMoa1207363.
72. Hawryluk GWJ, Aguilera S, Buki A, et al. A management algorithm for patients with intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). Intensive Care Med 2019;45(12):1783-1794. (In eng). DOI: 10.1007/s00134-019-05805-9.
73. American College of Surgeons Trauma Quality Improvement Program (ACS TQIP). Best Practices in the Management of Traumatic Brain Injury. 2015.
74. Peluso L, Lopez BM, Badenes R. Sedation in TBI Patients. In: Zhou Y, ed. Traumatic Brain Injury: Neurobiology, Diagnosis and Treatment2019.
75. Oddo M, Crippa IA, Mehta S, et al. Optimizing sedation in patients with acute brain injury. Crit Care 2016;20(1):128. (In eng). DOI: 10.1186/s13054-016-1294-5.
76. Flower O, Hellings S. Sedation in traumatic brain injury. Emerg Med Int 2012;2012:637171. (In eng). DOI: 10.1155/2012/637171.