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Monitoring of severe traumatic brain injuries in the neurointensive care unit

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The purpose of this review was to provide an overview of the recent studies discussing the current state of multimodality monitoring (MMM) of severe traumatic brain injury (sTBI) using both invasive and non-invasive techniques in neurointensive care. In addition, the latest randomized controlled trials RCTs on decompressive craniectomy (DC) for the management of refractory post-traumatic intracranial hypertension will be discussed.

A literature search was performed in PubMed, Scopus, Google Scholar and ISI Web of Knowledge for articles in English. The search included recent guidelines, meta-analyses, observational studies, RCTs, systematic and narrative reviews.

MMM, specifically, intracranial pressure (ICP) monitoring, brain tissue oxygen tension, pressure reactivity index, and cerebral microdialysis, are a promising group of techniques for understanding the complex pathophysiology following TBI. Invasive ICP monitoring is widely regarded as the most critical modality for the treatment of sTBI. Regarding non-invasive monitoring, optic nerve sheath diameter, near-infrared spectrometry and transcranial doppler have shown promising results. S100B could serve as a tool for MMM. In case of intractable ICP after failed maximal medical therapy, secondary DC should be considered as a life-saving option and should be made on a case-by-case basis.

We conclude that in isolation, no monitoring tool is likely to change outcomes, but when used as part of a goal-directed therapeutic strategy it could hypothetically influence outcomes. Critical care practitioners need to understand that these tools should be used in an integrated fashion, combining MMM data with the clinical examination, systemic monitoring, neuroimaging, and additional specialized monitoring tools.

Key words: traumatic brain injury, multimodality monitoring, intracranial pressure, decompressive craniectomy

Title: Monitoring of severe traumatic brain injuries in the neurointensive care unit

1. Summary

Traumatic brain injury (TBI) is concerned as one of the diseases with most complicated pathophysiology. The incidence of severe TBI (sTBI) is estimated to be 5.48 million each year and they account for around 10% of all TBIs. TBI severity classification is commonly based on Glasgow Coma Scale (GCS) and GCS score of 3 to 8 is considered as sTBI.

Classically, TBI is considered to consist of primary and secondary injury. Primary injury results instantly from physical force directed to the head. Secondary injuries develop after the impact with activation of multiple molecular and cellular pathways. Given that primary injuries cannot be reversed, the main goal of the management of sTBI is preventing deterioration arised from primary brain injury and preventing as well as reversing secondary brain injury ideally in a neurointensive care unit (NICU). These involve taking account systemic threats (e.g., hypotension, hypoxia, hypercapnia, hypoglycemia as well as hyponatraemia) and intracranial crises (e.g., increased intracranial pressure).

Recently, the approach of sTBI management has changed from monitoring intracranial pressure (ICP) alone to a multimodal approach, where cerebral perfusion pressure (CPP), median arterial pressure (MAP), brain temperature, brain tissue oxygen tension (PbtO2), and cerebral microdialysis are monitored simultaneously together with ICP. Monitoring ICP is commonly noticed as the most pivotal modality in the treatment of patients with sTBI. Monitoring of ICP is generally done by two ways, either via an external ventricular drain (EVD) or via intraparenchymal pressure transducers. Some non-invasive methods for example transcranial doppler as well as optic nerve sheath diameter are still being researched. In a case of refractory intracranial hypertension after adequate medical therapy is not succeeded, secondary decompressive craniectomy (DC) should be regarded as a last-tier therapy. Utilizing DC for refractory intracranial hypertension decreases mortality in sTBI and these patients are also more prone to recover compared to the patients treated with only medical management. Latest evidence suggests that secondary DC could be applied in the treatment of post-TBI intracranial hypertension, but it could lead to permanent harm for the patiens, for example severe disability. Hence, the decision to apply DC as last-tier management of sTBI should be considered thoroughly.

2. Introduction

2.1 Definition and brief epidemiology

TBI could be determined as a pathology of the brain or decreased brain function following head trauma (Menon et al., 2010). TBI, a diverse disease, is one of the most complex diseases known for its major economic and health related burden globally (Maas et al., 2008). The etiology of TBI consists of falls, traffic accidents, intentional self-harm, penetrating injuries, sport injuries and combat related events (Capizzi et al., 2020). The incidence of sTBI is 73 cases per 100,000 people worldwide which means about 5.48 million people every year. sTBI accounts for around 10% of all TBIs and 73% of all reported TBIs occur to males. According to the World Health Organization (WHO), nearly nine out of ten deaths as result of injuries occur in low- and middle income countries (LMICs) and TBIs represent half of those deaths. (Iaccarino et al., 2018). Patiens with sTBI are ideally treated in the intensive care unit (ICU) with a specialized expertise on neurointensive care.

2.2 Classification of TBI

Classification of TBI is usually done using one of four different domains (Fig 1.): clinical indices of severity, pathoanatomic type of the injury, physical mechanism of the injury or pathophysiology. Classification by injury severity (Table 1.) uses Glasgow Coma Scale (GCS), post-traumatic amnesia (PTA) and duration of loss of consciousness (LOC). The GCS score comprises values from three components: eye responses, verbal responses as well as motor responses and is put to use to assess the level of consciousness of the patient. TBI is generally classified as mild (GCS 13-15), moderate (GCS 9-12) and severe (3-8). (Maas et al., 2008). Although classification of TBI according to GCS remains a matter of debate, this has been vastly applied in the current literature. PTA is considered as the duration of time after initial injury where patient cannot produce new memories which could later be recognized. Classification of TBI by PTA score is mild (0–1 day), moderate (1-7 days) and severe (>7 days). Out of these two assessment methods of TBI severity, GCS is widely utilized in clinical use , but PTA is more infrequently used in clinical practice. (Hart et al., 2016).

TBI could be classified by pathoanatomic types as diffuse or focal brain injuries. Diffuse brain injuries cover diffuse axonal injury (DAI), cerebral edema as well as diffuse ischemic and injury of vasculture of the brain. DAI is a lesion that occur at the inter-faces of white and grey matter in TBI and is caused by shearing forces leading to axonal damage (Benson, 2014). Focal brain injuries include contusion, laceration and intracerebral hematomas (e.g. subdural hematoma, epidural hematoma, intracerebral hematoma and intraventricular hematoma)(Johnson et al., 2013). Physical mechanism of TBI classifies it into penetrating injury and closed injury.(Maas et al., 2008). According to the pathophysiological mechanism, TBI is generally split into two chronological stages: primary and secondary brain injury. This will be discussed in the next chapters of this literature review.

Table 1. Classification of traumatic brain injury severity

Criteria	Mild	Moderate	Severe
GCS	13-15	9-12	<9
PTA	0-1 day	>1 and <7 days	>7 days
LOC	0-30 min	>30 min and <24 h	>24 h
Imaging (CT)	Normal	Normal or abnormal	Normal or abnormal

Modified from: VA/DoD Clinical Practice Guideline for Management of Concussion/mTBI (2009).

GCS = Glasgow coma scale, PTA = Posttraumatic amnesia , LOC = Loss of consciousness,
TBI = Traumatic brain injury

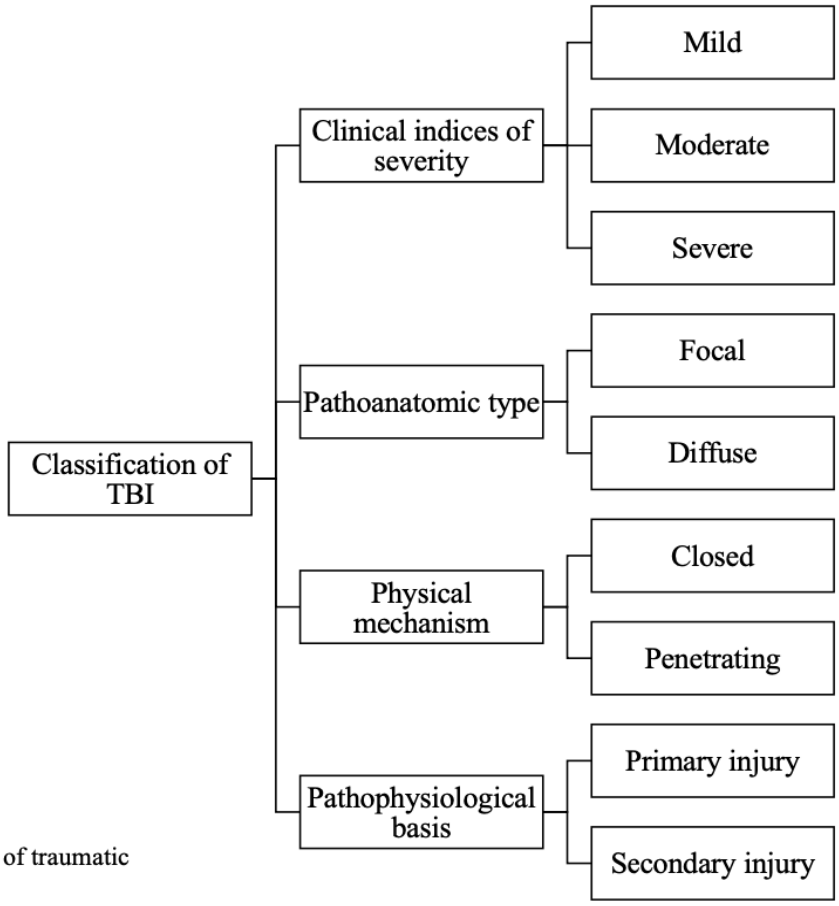

Fig 1. Classification of traumatic brain injury

2.3 Background of studying management choices for severe traumatic brain injury

TBIs represent the leading cause of disability as well as mortality worldwide among all of the injuries related to traumas (Iaccarino et al., 2018). The vast economic burden of TBI is evident: In the United States alone, annual costs of TBI is evaluated to be at least $ 90 billion and the cost per each patient is $ 396,000, when loss of productivity, costs of treatment and rehabilitation are taken into account (Laufer et al., 2022). These annual total costs are estimated to be € 33 billion in Europe (Olesen & Gustavsson, 2011). Annual costs of management of TBI in Finland is estimated to be approximately € 50 million (Tuominen et al., 2012). TBI also leads to significant loss on quality of life (Machamer et al., 2013.). The primary target of the management of TBI remains to prevent or even reverse secondary insults, maintain cerebral homeostasis and preserve rehabilitation potential. The management approaches, in order to prevent secondary injuries, include medical options and surgical interventions (e.g. mass lesion evacuation and/or decompressive craniectomy) as well as multimodality monitoring (MMM) utilized in the neurointensive care unit (NICU). Modern multimodality-based monitoring might lead to better outcomes after TBI through offering better understanding of pathophysiological mechanisms, thus, leading to more individually tailored therapies (Lindblad et al., 2022; Ruhatiya et al., 2020).

2.4 Aims of the study

The purposes of this thesis are:

- To provide an overview of the recent studies discussing the current state of multimodality monitoring (MMM) of sTBI using both invasive and non-invasive techniques.

- To discuss the latest randomized controlled trials (RCTs) on decompressive craniectomy (DC) for the management of refractory post- traumatic intracranial hypertension.

3. Primary and secondary injuries

Commonly, TBI could be categorized into two distinct stages: primary and secondary injury. Primary injury results instantly from physical force directed to the head, leading to possible fractures, hematomas, contusions as well as axonal injuries (Stocchetti et al., 2017).

Secondary injuries develop over time, usually within hours or days, after the initial trauma, with activation of multiple molecular and cellular pathways (Farooqui, 2018). When axons of the neurons stretch during injury, influx and efflux of transmembrane ions will be dysregulated, and axons will be vulnerable to demyelination and axotomy. This compromised permeability of neuronal cell membranes leads to increased influx of sodium (Na^+), efflux of potassium (K^+) and influx of calcium (Ca^{2+}). This process of increasing cytosolic calcium induces the release of neurotransmitters, particularly glutamate. When homeostasis of the cell gets impaired by TBI, uptake mechanisms will not work, leading to accumulation of glutamate in the cell (Farooqui, 2018). Glutamate attaches to NMDA-receptors, and this leads to further increases of cytosolic calcium by, for example, mitochondrial calcium which will lead to mitochondrial dysfunction and releases of free radicals. When increased, these contribute to peroxidation of lipids and impaired oxidative metabolism, which leads to further increases of lactate, acidosis of the blood, decreased cerebral blood flow (CBF),

edema and therefore, ischemia. (Pearn et al., 2017). These factors are considered to reflect the acute symptoms of TBI.

Microglial cells and astrocytes display significant influence in secondary injuries. After the initial trauma, microglial cells release cytokines that ignite inflammatory cascade leading to even more increased permeability through the BBB, decline in CBF as well as increased intracranial pressure (ICP). These result in further ischemia. Dead neural cells are not only lost and no longer functional, but also release substances toxic to neighbouring cells, augmenting the existing neuroinflammation. These processes, altogether, cause irreversible neuronal apoptosis leading to disturbed cerebral autoregulation (CA). CA could be defined as the ability of the cerebral vasculature to preserve adequate and steady intracranial blood flow as cerebral perfusion pressure (CPP) fluctuates (Silverman A & Petersen, 2023).

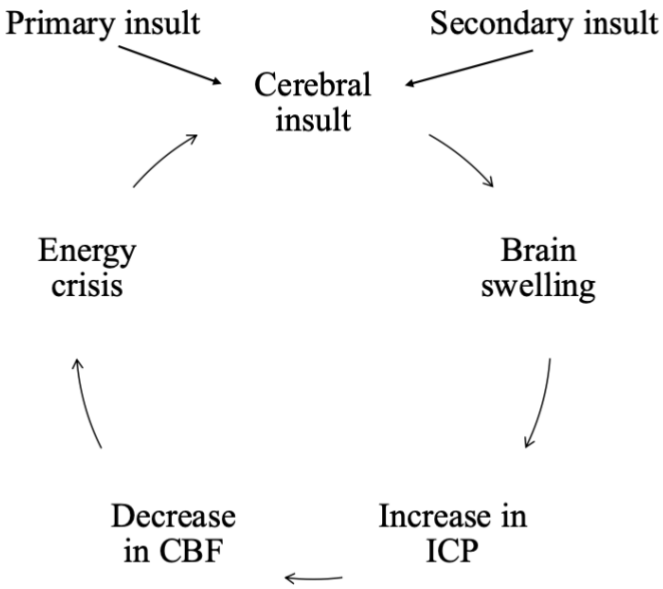

Fig 2. Escalating cycle of brain swelling following brain trauma

4. Cerebral autoregulation and energy crisis

4.1 Definition of cerebral autoregulation

As discussed in the previous chapter, CA is considered as the ability of the cerebral vasculature to preserve adequate intracranial blood flow as CPP fluctuates over time. In normal physiological conditions, CBF regulating involves changing the volume of arterioles, which, consequently, drive changes in resistance of vasculature of the brain. In TBI, this normal physiological function is impaired, leading to energy crisis in neuronal cells. CA is assessable by measuring the changes in CBF, CPP or mean arterial pressure (MAP).(Silverman A & Petersen, 2023).

4.2 Impairment of cerebral autoregulation after severe traumatic brain injury

Four main mechanisms contribute to the CA. The vasculature of brain has ability to change its tone based on increase or decrease in pressure. This is feasible as a result of smooth muscle cells' ability to contract and relax. Alternatively, neurogenic response is the ability of neuronal cells to excrete vasogenic neurotransmitters. The metabolic mechanism, which influences autoregulation, operates mainly in capillaries. Carbon dioxide (CO2) subsequently modifies vasomotoric responses, with each one mmHg rise in partial pressure of carbon dioxide associated with approximately four percent increase in CBF (Yoshihara & Bandoh, 1995). The endothelial mechanism involves the endothelial layer of the vessels. Through this mechanism, the endothelium secretes vasodilatators and vasoconstrictors (Silverman A & Petersen, 2023).

One of the most significant consequences of sTBI is the disruption of the BBB, which refers to tightly interconnected endothelial cells in cerebral vessels responsible for regulating the exchange of substances between blood and brain tissue. However, following sTBI, the compromised BBB can lead to secreting of inflammatory and vasoactive substances which further dysregulate cerebral blood flow. Additionally, the neurogenic response, which involves the release of vasoactive neurotransmitters, may also be affected by sTBI. Damage to neurons and their communication pathways can lead to an altered secretion of these neurotransmitters, leading to abnormal vascular responses. Cellular damage and altered metabolism in the brain tissue may lead to inadequate regulation of local CBF, aggravating the cerebral autoregulatory dysfunction. These direct effects on autoregulatory mechanisms in sTBI leads often to changes in ICP. (Zeiler et al., 2020).

4.3 Energy crisis in severe TBI

All abovementioned impairments of autoregulation, together with factors contributing to secondary injuries, can lead to energy failure within the neuronal cells. Swelling of the brain after head trauma is commonly referred to cytotoxic edema which might result either from declined energy supply for the brain or surged energy requirements caused by TBI. Hypotension and hypoxia are also crucial for leading to insufficient delivery of oxygen and vital subtances to the brain. Moreover, impaired energy generation is facilitated by various additional factors, including tissue hypoxia due to compromised oxygen diffusion, ischemia in microvasculature, or mitochondrial dysfunction resulting in metabolic energy crisis. In addition, it has been also studied that metabolic energy deficit of the brain may result from insufficient delivery of glucose or from the failure of the neuronal cells to use glucose properly (Menon & Ercole, 2017).

Above mentioned models of energy crisis have related consequences for metabolic markers, with elevated lactate levels and lactate/pyruvate ratio (LPR) measurable with microdialysis (Menon & Ercole 2017). Elevated need for energy can also result from seizures that are detectable by electroencephalography (EEG). These multimodality approaches for identifying and assessing energy crises caused by TBI will be discussed in chapter 5

4.4 How do we prevent and treat further secondary injury?

Maintaining adequate CPP and optimal ICP are the cornerstones for preventing secondary injuries following sTBI. An optimal CBF ensures a sufficient cerebral glucose and oxygen delivery, essential for neuronal metabolism and function. CPP needs to be maintained within suitable ranges to avert the consequences of hypo- or hyperperfusion, both of which are associated with poor outcome (Menon & Ercole 2017). An appropriate MAP ensures stable cerebral hemodynamics supporting proper blood flow to the brain parenchyma. Ideal management of ICP ensures adequate cerebral perfusion and prevent ischemia. These factors are monitored in NICU using multimodal techniques discussed in chapter 5. Early detection of changes in these vital parameters enables immediate interventions to maintain cerebral hemodynamics.

In brief, the management strategies include neutral head position, elevating the head to 30 degrees, pain relief and sedation, glycemic control, electrolyte control, temperature control and seizure prophylaxis. These are common for almost all TBI patients (Hossain et al., 2023; Schizodimos et al., 2020). Acute, step-by-step escalation of interventions consist of hyperosmolar therapy, sedation of the patient and medical analgesia , usage of barbiturates, hyprerventilation in order to lower ICP, therapeutic hypothermia, drainage of cerebrospinal fluid (CSF) and, lastly, secondary DC (Helmy et al., 2007; Hossain et al., 2023; Schizodimos et al., 2020). Previously mentioned strategies are elaborated in chapter 9.

5. Monitoring of severe TBI

5.1 Intracranial pressure

ICP could defined as increased pressure directed to the brain parenchyma by blood and CSF (Czosnyka, 2004). It is a significant and potentially fatal complication of sTBI unless treated in time. The Monro-Kellie doctrine declares that overall volume of contents inside the skull persists stable because of enclosured skull. Consequently, when there is an increase in CBV caused by vasodilation, accumulation of water outside blood vessels due to a disrupted BBB, swelling of cells, or the presence of mass lesions, brain tissue as well as CSF volumes are compromised. If the volume inside the skull increases beyond compensatory capacities, the ICP elevates. (Stocker, 2019).

Most broadly recognized threshold for ICP to begin therapy is 20 mmHg, whereas the most recent Brain Trauma Foundation (BTF) guidelines advise the threshold to be 22 mmHg (Carney et al., 2017; Menon & Ercole, 2017). Most recent guidelines from The BTF advocate to monitor ICP among all patients with sTBI (GCS 3-8 after resuscitation) with positive computed tomography (CT) imaging. Additionally, monitoring of ICP is also indicated in sTBI patients with negative CT scan if 2 or more of the following criteria are demonstrated at the time of admission: over 40 years of age, systolic blood pressure is below 90 mmHg or patient has uni- or bilateral motor posturing. (Carney et al., 2017).

Recently, the Intracranial pressure monitoring in patients with acute brain injury in the intensive care unit (SYNAPSE-ICU) study has provided evidence that ICP monitoring might be associated with more intensive therapeutic approach and with lower six-month mortality in more severe cases (Robba et al., 2021).The profound evidence of ICP as predictor of outcome and its ability to detect and monitor episodes of intracranial hypertension has secured its essential role in the treatment of TBI patients (Balestreri & Czosnyka, 2006). Time-average of ICP waveform, mean ICP, consists of three

different components- respiratory waveform (P1), pulse pressure waveform (P2) and slow vasogenic waveform (P3). Increased ICP alters these waveforms and therefore interpretation of ICP waveforms could bring clinical benefit to management of increased ICP. (Harary et al., 2018). Three primary approaches are employed in the management of increased ICP: traditional approach targeting ICP, CPP-targeted therapy and the volume-targeted treatment approach (Lund concept) (Grande, 2017; Stocker, 2019). Management of sTBI is discussed in chapter 9. Secondary DC as a treatment of intractable ICP is discussed in chapter 10.

5.1.2. Invasive and non-invasive monitoring of ICP

Monitoring of ICP invasively is crucial part of the management of sTBI. The well-known invasive ICP measurement methods typically consists of ventricular catheters or intraparenchymal bolts inserted inside the skull. However, non-invasive methods, for example, optic nerve sheath diameter (ONSD) measurement with ultrasonagraphy or transcranial doppler (TCD) have also shown promises (Wijayatilake et al., 2015). ONSD measurement is based on the alterations in the diameter of protective sheath enveloping optic nerve. In situations with increased ICP, the diameter of the optic nerve sheath increases. For dynamic estimation of ICP levels from all non-invasive methods, ONSD is suggested to be the leading modality.It is applicable for triage in emergency settings, but it is not suitable for continuous bedside measuring (Richards et al., 2023). TCD will be discussed in chapter 5.8 for its ability to measure CPP. TCD is also capable to estimate levels of ICP. It is cost-effective, non-invasive, effortless to administer, and replicable. However, its most significant limitation is user dependency in interpretation, but this limitation is expected to be addressed with the use of robotic technologies in the future.

Table 2: Invasive and non-invasive intracranial pressure measuring.

	Inasiveness	Continuous monitoring
Intraparenchymal bolt	Invasive	Yes
External ventricular drain	Invasive	Yes
Optic nerve sheath diameter	Non-invasive	No
Transcranial doppler	Non-invasive	No

Modified from: Non-invasive Intracranial Pressure Monitoring (Muller et al., 2023)

5.1.3 Intraparenchymal pressure transducers

Intraparenchymal pressure transducer (commonly abbreviated ICPM, “ICP monitor”) is a catether or a probe, which is installed into cerebral parenchyma via incision and a drilled hole in the NICU. Compared to external ventricular drain (EVD) for measuring ICP, intraparenchymal pressure transducers are less invasive and have a lower risk of infection. Moreover, their placement is comparatively simpler than EVD, since it does not necessitate a procedure in the operating room. (Menon & Ercole 2017).

5.1.4 External ventricular drain

A closed EVD is regarded as the most approved technique for measuring ICP and draining CSF (Lindblad et al., 2022). EVD is a medical device comprising a catheter installed into CSF-filled ventricle. This enables continuous measurement of ICP or the drainage of excessive CSF volume to decrease elevated ICP. However, it is noteworthy that EVD bears a higher risk profile compared to intraparenchymal pressure transducers, as it is associated with infection rates of approximately 10%, while the latter exhibits 1% infection rate (Tavakoli & Peitz, 2017).

5.2 Cerebral blood flow

Ischemia is an ordinary and detrimental secondary injury following TBI. Brain parenchyma cannot reserve oxygen for longer period of time than a few seconds, since brain’s adenosine triphosphate reserves will only last around 40 seconds during complete ischemia. (Rostami et al., 2014). CBF refers to blood volume (mass) that flows in brain tissue per time. Various monitoring techniques have been used to measure CBF in clinical settings. These methods consists of TCD and Near-infrared spectroscopy (NIRS) (Fatima et al., 2019; Lindblad et al., 2022). These both methods are to be discussed in the following chapters. While additional modalities, for instance xenon-CT and positron emission tomography (PET) exist for measuring CBF, their applications within clinical settings are limited (Fantini et al., 2016). Crucial cererbral oxygen supply is dependent of CBF. After initial trauma, cerebral autoregulation is often at least partially impaired, leading to increased blood pressure in arteries, subsequently leading to surge in CBV and CBF and, eventually, in ICP. Consequently, CBF needs to be maintained at adequate level since insufficient CBF leads to oxygen and nutrient deprivation to the brain while excessive CBF cause complications and elevate ICP (Stocker, 2019).

5.3 Cerebral perfusion pressure

CPP represents pressure between MAP and ICP. Therefore, formula for calculating CPP is MAP-ICP and this is usually calculated automatically by bed-side monitors in NICU (Fantini et al., 2016; Stocker, 2019). Because the management of sTBI relies on decreasing increased ICP and optimizing faulty CPP, this parameter is vital for maintaining adequate blood supply to the brain, hence ensuring sufficient oxygenation and glucose delivery, consequently preventing secondary injuries. Uniform CPP targets for CPP-targeted therapy have not yet been established and the current targets are not based on high-quality evidence. However, consensus according to the BTF guidelines and The Seattle International Brain Injury Consensus Conference (SIBICC), for minimal CPP threshold is 60 mmHg (Carney et al., 2017; J Hawryluk et al., 2019). Current discussion on this subject acknowledges the

most favorable target for CPP to be different for each patient. In addition, BTF guidelines suggest that aggressive interventions for maintaing CPP over 70 mmHg is inappropriate due to potential cardiopulmonary (especially acute respiratory distress syndrome) complications associated with fluid loading (Carney et al., 2017). Furthermore, CPP above 70 mmHg have not offered any outcome benefits according to a study and therefore CPP levels above that should be avoided (Guy L & Miller, 2002; Stocker, 2019).

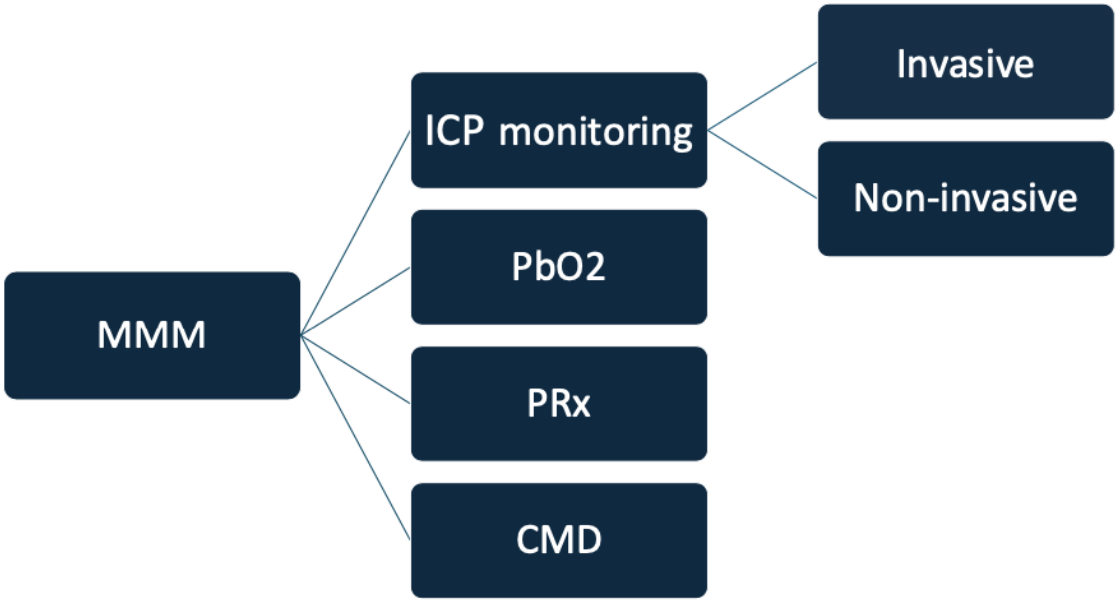

Fig 4. Diagrammatic presentation of different ways of neuromonitoring

5.4 Pressure-reactivity index

Pressure-reactivity index (PRx) is considered as correlating factor between pressure of the arteries and ICP. Negative values of PRx indicate preserved cerebral vascular reactivity. In this condition, when blood pressure rises, compensatory vasoconstriction occurs to sustain a sufficient level of CBF. Conversely, PRx values that are positive, indicate faulty vascular response. In this state, elevated MAP lead to "passive" dilation in arterioles and to elevation in cerebral CBV, which results in increase of ICP. (Timofeev et al., 2011). Therefore, PRx is a valuable tool for monitoring cerebral autoregulation and TBI treatment in NICU may be individualized for the patients by determining optimal CPP (CPPopt) based on PRx. PRx is a global parameter, and therefore if autoregulation is impaired regionally, it might not be able to detect it (Stocker, 2019).

PRx ranges from zero to one, where zero indicates optimal CA and one suggests totally impaired autoregulation of CBF. BTF guidelines state that a PRx levels over 0.25 associate with increased mortality and PRx over 0.05 with unfavorable outcome (Lindblad et al., 2022). While PRx and CPPopt are not yet regarded as clinically usable guides for maintaining cerebral autoregulation, emerging evidence suggest that treatment of sTBI in NICU could include PRx-targeted treatment and PRx has clinical significance (Menon & Ercole, 2017.; Posti et al., 2021).

5.5 Optimal cerebral perfusion pressure

It is observed that over extended time periods, PRx shows U-shaped correlation with CPP, which is graphical presentation of the range of autoregulation, suggesting the existence of CPPopt, in which CPP is considered optimal when PRx is at its lowest, indicating the preservation of optimal autoregulation (Menon & Ercole 2017.; Tas et al., 2021). Research has provided evidence that preserving CPP within or near to this optimal range for autoregulation might lead to improved outcome of the patient (Aries et al., 2012). In recent TBI algorithms, the recognition of CPPopt as a vital parameter has led to its integration, considering the individual variability in target levels. (Menon & Ercole, 2017).

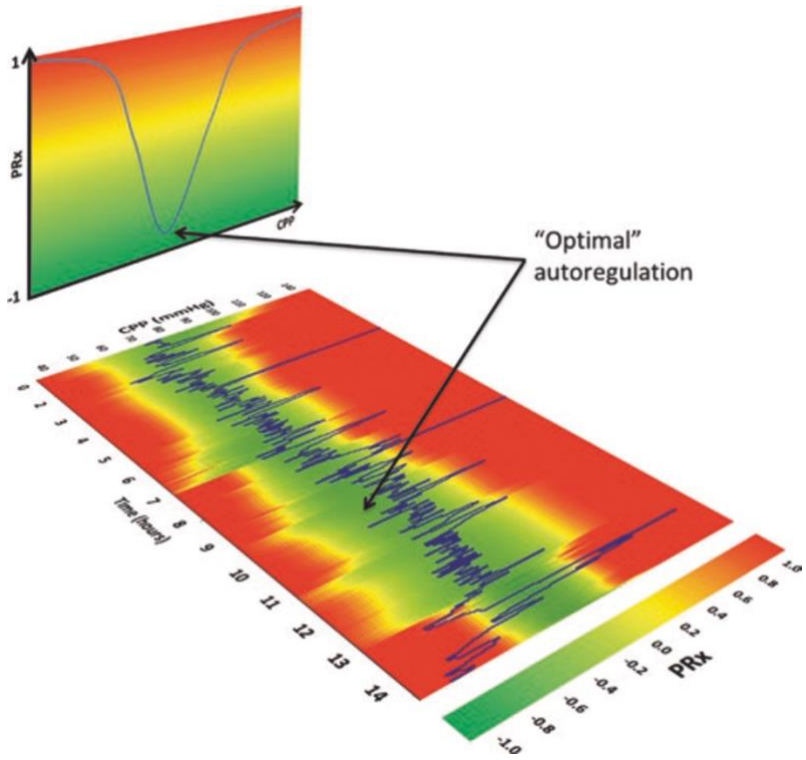

Fig 3. Optimal cerebral autoregulation (Menon & Ercole, 2017). (Reprinted with permission)

5.6 Brain tissue oxygen tension measurement

Cerebral oxygenation can be monitored bed-side. It is typically done using two invasive methods: direct brain tissue oxygen tension measurement (PbtO2) and jugular venous bulb oximetry. NIRS is another, non-invasive, bed-side monitoring modality for cerebral oxygenation, but there is consensus that it has excessive limitations for its utility in clinical settings, the ischemic thresholds are yet to be defined and no studies currently indicate that NIRS data could independently have effect on the outcome after TBI. (Le Roux et al., 2014).

PbtO2 is considered as the golden standard for bed-side monitoring of cerebral oxygenation (Patchana et al., 2020). It is invasive, focal continuous monitoring method with low complication rate. Because

it measures focal oxygenation, its utility is dependent on the probe location. Most frequently utilized technology for measuring PbtO2 is Clark electrode (e.g., Licox), which measures PbtO2 by using oxygen sensor which identifies flux of oxygen through membrane, generating electrical current proportional to the oxygen partial pressure in brain. (Le oux, 2013). The latest BTF guideline suggested threshold for PbO2 is considered as 20 or 22 mmHg (Carney et al., 2017). According to Brain Tissue Oxygen Monitoring and Management in Severe Traumatic Brain Injury (BOOST-2) trial, management protocol where PbtO2 is monitored together with ICP, decreased cerebral hypoxia following sTBI, leading towards improvement in outcome (Okonkwo et al., 2017). Also, the SIBICC consensus states that PbtO2 should be concerned as the second monitored variable after ICP (Chesnut et al., 2020)

5.7 Cerebral microdialysis

Cerebral microdialysis (CMD) measures brain chemistry and it is able to indicate optimal CPP levels among TBI patients (Stocker, 2019). It is currently utilized in routine intensive care at 30 academic centers globally (Stovell et al., 2023). CMD sensors a variety of energy metabolites, such as lactate, glucose, glycerol, glutamate and pyruvate (Timofeev et al., 2011). CMD involves a catheter attached into cerebral parenchyma. This catheter sensors the osmotic flux of the substances through membrane. As a result, above mentioned metabolites can be measured bed-side, usually each hour (Hutchinson et al., 2015). CMD measures also crucial derived ratios such as lactate / glutamate (LGR) and LPR. LPR indicate oxidative metabolism of the brain and its levels elevate if the glycolysis cannot take place for the lack of oxygen or for another factor interrupting mitochondrial respiratory chain. Consequently, LPR (threshold >25) serves as a marker for brain tissue ischemia (Timofeev et al., 2011). CMD glucose (threshold <2.0) is reduced in patients with sTBI and continuously low concentrations are considered to be associated with poor outcome. CMDs limitations include that it is a laborious modality, focal measurement and its data cannot be interpreted instantly. Current guidelines from Neurocritical Care Society and the European Society of Intensive Care Medicine suggest monitoring CMD in patients who might suffer from cerebral ischemia, cerebral hypoxia, deficit of energy or deficit of glucose, together with clinical indicators and monitoring (Le Roux et al., 2014). CMD hold promises for increased utilization in the management of TBI for addressing the evolving abnormalities in cerebral physiology, however, still not widely used as a part of clinical practice globally (Stovell et al., 2023).

5.8 Transcranial doppler

TCD is able to monitor ICP and CPP real-time. It is non-invasive and it allows CBF monitoring to be conveniently conducted at bed-side (Moreno et al., 2000). TCD offers cost-effective and low-risk solution for bedside monitoring, and it is suitable for emergency settings (Naqvi et al., 2013). However, it has limitations in clinically approved TBI management. These consist of operator dependency, limited resolution, limited accuracy on estimating vessel diameters based on TCD. Medications, autoregulation as well as hyperemia can influence CBF, consequently affecting the measurements done by TCD. In addition, TCD's reliability is compromised if the patient's acoustic temporal window is deficient. (Fatima et al., 2019). The latest BTF guidelines do not recommend TCD in monitoring of TBI patients due to insufficient research evidence. (Carney et al., 2017). However, future development of robotic TCDs holds a promise in reducing its user-dependency, thus enhancing its potential as longitudinal assessment method (Zeiler & Crit Ultrasound, 2018).

5.9 Electroencephalography

EEG is a monitoring modality used in ICU to monitor seizures. Seizures are common complications following TBI and they typically remain undetected in the absence of adequate monitoring methods. These seizures are treatable and that indicates the utility of EEG monitoring of TBI patients. Furthermore, notably up to 50% of patients with TBI exhibit cortical spreading depolarizations that can be detected through EEG and are associated to unfavorable outcomes (Meyfroidt et al., 2022). Advanced EEG techniques have already successfully identified brain activation and responsiveness of comatose patients and therefore EEG could be helpful monitoring method in guiding interventions of TBI patients. (Meyfroidt et al., 2022). SIBICC guidelines suggest utilizing EEG as monitoring method for inter-tier evaluation of TBI patients (Chesnut et al., 2020). Scalp EEG is noninvasive, inexpensive and it reacts to intracerebral alterations, for example, in ischemia, but it is not able to identify above mentioned cortical spreading depolarizations and therefore invasive, and more expensive EEG might be needed (Carandang, 2015). However, invasive EEG can lead to adverse events, such as cerebral infections and intracranial hemorrhage (Shah & Mittal, 2014).

5.10 Neuroimaging

5.10.1 Computed tomography

CT is considered as the primary imaging modality performed in acute phase of TBI and it is widely recognized as a golden standard in TBI diagnostics (Figueira et al, 2020). CT allows a clinician to objectively assess the physical damage of the brain parenchyma caused by TBI. (Maas et al., 2007). CT is suitable imaging technique for evaluation of neurocritical patients in NICU in the acute phase (Bhargava, 2019). Parenchymal mass lesions are typical consequences of TBI and they occur even in 13-35% of sTBI cases (Iaccarino et al., 2014). These lesions are commonly noticed with routine CT scans.

Several factors advocate using CT in acute stage following TBI. CT represents a rapid modality which is regularly used in emergency settings and is widely available. It can be used in triage and as a follow-up modality as it is fast and able to detect both primary as well as secondary injuries (Lolli et al., 2016; Schweitzer et al., 2019). CT remains as superior modality for depicting brain injuries that need acute neurosurgical intervention, such as hemorrhage, infraction and herniation (Schweitzer et al., 2019). CT scans are cost-effective and relatively easy to interpret. Also, monitoring of critically ill patient during CT scan is feasible without need for specialized arrangements. Modern CT imaging capabilities have brought new possibilities in terms of imaging of head trauma patients. These imaging modalities are CT angiography (CTA), CT perfusion imaging and three dimensional reconstructions. CTA is used to uncover vascular lesions following head trauma, but its routine use in acute phase is not preferred. CT perfusion imaging is routinely utilized in the setting of stroke, but it is also under research for a tool in TBI diagnostics and monitoring (Douglas et al., 2018)

However, CT scans have multiple limitations as a diagnostic tool. It has limited sensitivity and therefore, it leads to number of false-negatives scans, possible with a life-threatening complications such as delayed intracranial hemorrhage. CT scans may also have temporal delay behind actual intracranial damage, hence examinations within 3 hours of trauma may potentially result in underestimation of the severity of the injury. In addition, CT's sensitivity for detecting microhemorrhage or diffuse axonal injury (DAI) remains limited. (Amyot et al., 2015). CT involves radiation exposure which limits its utility in follow-up monitoring. Radiation exposure of one head

CT imaging is equivalent to approximately 70 chest X-rays. Pregnancy is contraindicated for the use of CT, unless patient has a life-threatening emergency. In addition, CT is not preferred choice of imaging for TBI in children for high radiation exposure.

5.10.2 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is used as a supplementary imaging method to CT and it is indicated in acute setting of TBI when head trauma patient has persistent neurological deficit not explained by primary CT scan (H. Lee et al., 2021). MRI has higher sensitivity for axonal injuries (e.g. DAI), microhemorrhage, small contusions and blood products for 1-2 days after onset of the trauma. It is considered that from 48 to 72 hours after trauma, MRI remains preferable to CT, for its ability to detect intracerebral hematomas enhances gradually compared to CT. (B. Lee & Newberg, 2005). Diffusion tensor imaging (DTI) is a MRI based imaging modality that is capable of visualizing white matter tracks and is therefore sensitive to microstructural axonal injury not seen in conventional MRI or CT (H. Lee et al., 2021). However, DTI is still not applicable in clinical use yet although the method shows promise in identifying patients with mild TBI at risk for long-term deficits (Richter et al., 2024). MRI has its limitations such as speed, accessibility, sensitivity to motion of the patient and higher costs compared to CT, decreasing its utilization in NICU in the acute phase (B. Lee & Newberg, 2005). It also has its own limitations of safety concerns because metallic foreign bodies (Schweitzer et al., 2019).

5.11 Brain temperature

Normally, brain temperature is between 36°C–37.5°C and it is maintained through thermoregulation process by hypothalamus (Wang et al., 2016). After TBI, thermoregulation process might get impaired, leading to abnormal brain temperatures. TBI can induce both, hyperthermia and hypothermia. Broad research has demonstrated benefical effects of mild hypothermia (32°C–35°C) on neurological recovery after cardiac arrest. Therefore, therapeutic hypothermia has been recognized as potential management method also in TBI (Jo, 2022). In induced hypothermia, core temperature of patient is lowered below normal, to 32°C–35°C, in order to decrease CBF and metabolism of the brain, resulting in decreased ICP. At cellular level, haphazard flux of electrocytes through cell membranes of neurons ceases and cerebral edema reduces (J. Kim et al., 2020). As a result, hypothermia leads to a neuroprotective effect. Complications of therapeutic hypothermia include bradycardia, electrolyte disorders, coagulation disorders, pulmonary infections and hypotension (Andrews et al., 2018). In recent years, numerous studies have been conducted about hypothermia for intracranial hypertension and there lies a debate if hypothermia should be induced as a prophylactic management or as last-tier option to refractory ICP. Large Eurotherm3235 RCT showed that participant group that went under hypothermia management, had successfully reduced ICP, but had increased mortality as well as decreased functional recovery after six months of follow-up (Andrews et al., 2018). This study provided evidence against initial use of hypothermia in ICP management, but it did not provide evidence against its use in refractory ICP. In addition, many studies indicate that utilizing hypothermia in the management of TBI may be favorable for the patient, when only few alternatives remain (O'Leary, 2016). Thus, therapeutic hypothermia for managing elevated ICP in NICU settings remains matter of debate.

6. Body fluid biomarkers

Blood based biomarkers show significant potential as a method for improved TBI diagnostics and prediction of outcome together with imaging findings, monitoring and clinical parameters. Various potential biomarkers have already shed evidence for possibly being clinically relevant but attaching these into clinical settings remain unsuccessful. Significant individual variations among patients with TBI, concerning these biomarkers, pose a major challenge. These variations are influenced by, for example, age, integrity of BBB and functioning of kidney and liver. Another critical challenge arises due to the effect of sampling timing and analytical methods on the diagnostic performance of biomarkers. Adequate specific and sensitive biomarkers, able to detect the presence and severity of TBI, predict the progression of the disease and improve outcome predictions, remain still in demand (Posti & Tenovuo, 2022).

Recently, the most studied biomarkers in TBI are glial cell injury biomarkers S100 calcium-binding protein B (S100B) and glial fibrillary acid protein (GFAP), axonal injury biomarkers neurofilament light (NF-L) and Tau, as well as neuronal cell injury biomarkers neuron specific enolase (NSE) and Ubiquitin C-terminal hydrolase-L1 (UCH-L1) (Ghaith et al., 2022). TBI and ischemia activates astroglial cells to release S100B protein in to extracellular space, and, consequently to the bloodstream from where concentration of the biomarker can be measured using simple blood sampling. Numerous research findings strengthen the evidence that elevated S100B levels have been associated with increased severity, mortality and unfavorable outcomes, indicating its potential when used as a part of continuous monitoring. Nevertheless, many studies have reported that S100B exhibits limited predictive value, particularly concerning long-term outcome prediction and S100B has also extra-neural sources which limits its use in clinical settings in case of polytrauma. GFAP originates from astroglial cells following TBI, in order to induce formation of scar tissue in glial cells. TBI exacerbates release of GFAP, leading to increased levels that could be measured from the blood (Yang & Wang, 2015). Studies show positive correlation between levels of GFAP and severity of TBI (A Retel Helmrich et al., 2022). Lately, TRACK-TBI group reported that plasma GFAP could provide one of the most useful prognostic information for mortality and poor outcome in case of moderate to severe TBI (Korley et al., 2022).

NF-L is a subunit of a neurofilament protein, that undergo phosphorylation under normal conditions. After TBI, intracellular calcium increases and activates cascades leading to dephosphorylation, proteolysis, and dissociation of NF-proteins which can subsequently be measured from CSF and blood. The release of NF-L continues for several days after onset of the trauma. Various study findings indicate that NF-L levels elevate during the first two weeks after sTBI, indicating poor outcome for the patient. Levels of NF-L have also been shown to be able to do outcome prediction at 12 months. (Ghaith et al., 2022). BIO-AX-TBI study showed that measured NF-L levels might correlate with the damage of cerebral white matter after TBI (Graham et al., 2021). Therefore, NF-L could be a useful biomarker for prediction of patient outcomes in TBI.

Ubiquitin C-terminal hydrolase-L1 (UCH-L1) is a cytoplasmic enzyme of neurons. It participates in clearing abnormal neuronal proteins (Mehta et al., 2020). Increased serum UCH-L1 is associated with disturbed BBB function following moderate and severe TBI (Mehta et al., 2020). Current evidence indicates that concentration of serum UCH-L1 following head trauma correlates with the severity of the injury and outcomes, including CT-positive lesions and admission score of GCS. Therefore UCH-L1 is considered as potential fluid TBI biomarker for its prognostic and diagnostic abilities. (Hossain et al., 2024). The most recent statement from CENTER-TBI study shed robust evidence that integration of UCH-L1 in prognostic models, IMPACT and CRASH, have additional prognostic value regarding functional outcome after TBI. (A Retel Helmrich et al., 2022).

Primary injury promotes neuroinflammatory response, thus accelerating secondary injuries and brain swelling. Inflammasomes play crucial role in this inflammatory response, and these proteins are associated with worse functional outcome. Therefore, inflammatory biomarkers may be used as promising biomarkers in TBI to explore the reasons behind increased ICP. According to previous studies, the most reliable inflammatory biomarkers include the apoptosis-associated speck like protein (ASC), tumor necrosis factor (TNF)-α, IL-4 and IL-6 and IL-18 (Johnson et al., 2022).

Blood biomarkers could theoretically help stratify severities of TBI, but evidence about this remain limited. Current results from CENTER-TBI study show, that GFAP levels measured during the initial 12 hours after onset of the trauma, could detect CT positivity (Czeiter et al., 2020). GFAP could assist on stratifying patients for advanced imaging in ICU and could assist to avoid potential transfer related complications (Richter et al., 2022). To date, S100B has been recognized to be applicable for monitoring sTBI patients in the NICU, suggesting that biomarkers could, therefore, be used as a complement to monitor TBI in the NICU (Korfias et al., 2007; Thelin, 2016; Thelin et al., 2017). According to recent studies, S100B appears also to be positively correlated with elevated ICP levels, contributing to a better understanding of ICP elevations (Ghaith et al., 2022). Even minor increases of S100B have strong sensitivity and specificity detecting imaging positive lesions in brain parenchyma (Lindblad et al., 2022). Regarding to outcome prediction, applicable biomarkers include mainly NF-L, especially to explore DAI. (Mondello et al., 2011; Welch et al., 2017),(Hossain et al., 2019). As yet, BTF guidelines do not include blood biomarkers (Lindblad et al., 2022).

7. Medical and surgical management of severe traumatic brain injury

Management of sTBI in NICU is currently based on supporting vital functions in an effort to lessen or even revert secondary injuries caused by TBI. These injuries may be provoked by systemic disturbances or intracranial causes. Most crucial parts of neurocritical care are ICP control and CPP maintenance, and therefore, both medical and surgical approaches, are employed to address these critical aspects. The following strategies are based on the latest BTF guideline (4th edition, 2016) and are part of the Addenbrooke's Hospital (Cambridge, UK) sTBI protocol (Menon & Ercole, 2017).

7.1 First-line strategies

7.1.1 Ventilation

Endotracheal intubation and mechanical ventilation are commonly used crucial methods for airway protection after TBI, especially in a case where patient has reduced consciousness. In addition, these secure adequate pulmonary ventilation in order to stabilize arterial oxygen and carbon dioxide tension, which plays important role since carbon dioxide vasodilatates cerebral arteries and therefore hypercapnia increases ICP. Contrarily, hypocapnic vasoconstriction leads to reduction in ICP. Therefore, as latest BTF guideline suggest, hyperventilation can be used as a temporary method for ICP reduction. Prolonged prophylactic hyperventilation with partial pressure of carbon dioxide of below or 25 mmHg is not recommended. Optimal saturation level of oxygen is between 94-96% (Yin et al., 2022). Moreover, research evidence suggest to avoid hyperventilation within the initial 24 hours after the trauma for then CBF is typically critically reduced. However, if hyperventilation is still utilized, jugular bulb venous oxygen saturation (SjO2) or PbtO2 measurements are preferred for monitoring oxygen supply. (Carney et al., 2017).

7.1.2 Sedation

Sedation is commonly employed during the first stages of sTBI. Commonly, the primary approach for sedative agent is propofol or a benzodiazepine (Menon & Ercole, 2017.). Propofol costs more and causes hypotension more than benzodiazepines. It reduces CBF and ICP, as well as increases seizure threshold. Benzodiazepines reduce CBF and ICP as well, but they are not as potent as propofol in this regard. However, benzodiazepines exhibit a longer context-sensitive half-life compared to propofol. It is recognized, that effectiveness of both agents for controlling ICP is comparable, but midazolam is inferior to propofol at controlling refractory intracranial hypertension. Range of opioids (e.g. remifentanil) can be used as complementary for sedation in the setting of sTBI. (Menon & Ercole, 2017). According to BTF guidelines, propofol is not recommended for reducing mortality or improving outcome at six months, although is is recommended for ICP controlling. If ICP remains increased despite of maximal standard medical and surgical treatment, administrating high-dose of barbiturates is recommended. Complications of barbiturates include hypotension, coma and respiratory depression. Before and during the barbiturate treatment, it is crucial that patient's hemodynamic status must be stabilized. (Carney et al., 2017).

7.1.3 Blood glucose

Hyperglycaemia at admission, is associated with unfavorable outcome. Yet, too strict glycaemic control might lead to seriously lowered levels of glucose in the brain and to unfavorable outcome. (Menon & Ercole, 2017). Hence, the aim of blood glucose management in TBI is to prevent both, hyper- and hypoglycemia, while ensuring an adequate supply of cerebral glucose. Latest BTF guidelines do not have recommendations for glucose control, for the lack of consistency in research findings covering this subject.

7.1.4 Temperature management

Managing temperature in patients with TBI involves addressing three primary concerns: applying therapeutic hypothermia as neuroprotective measure, inducing hypothermia for reducing intracranial hypertension, and actively preventing hyperthermia (i.e. controlling of fever). Despite of the supportive evidence from previous research about therapeutic hypothermia, recent multicenter trials (Zygun et al., 2011) have not succeeded to show favorable evidence on cooling to 32-34 C and the findings of recently published systematic review (Saxena et al., 2014) suggests that less intensive hypothermia is not benefical. It is recognized that therapeutic hypothermia can lower increased ICP, but recently published Eurotherm3235 Trial could not show evidence of benefit of cooling the patient in order to maintain ICP levels under 20 mmHg, which is widely regarded ICP threshold for therapy. Another finding of this study was, that although ICP was lowered efficiently with therapeutic hypothermia, it caused poorer functional outcome and increased mortality for the patients.(Andrews et al., 2018). The Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury-Randomized Clinical Trial (POLAR-RCT) provided evidence that early hypothermia used as a prophylactic measure could not enhance neurological outcomes at six months when compared to normothermia (Cooper et al., 2018). The latest BTF guidelines suggests that early or short-term hypothermia is not recommended as prophylactic measure to enhance outcomes in patiens who suffer from diffuse injury (Carney et al., 2017).

7.1.5 Seizure prophylaxis

Various guidelines recommend to decrease early seizures following TBI in risk patients with a one week antiepileptic drug treatment. These therapies include administration of, for example, phenytoin, valproate and levetiracetam. Early (within seven days) post-traumatic seizures are recommended to treat with phenytoin therapy, although it could lead to adverse drug reactions. Additionally, BTF guidelines suggest against treating late post-traumatic seizures prophylactically with valproate or phenytoin (Carney et al., 2017). Ongoing Management of Seizures after Traumatic Brain Injury (MAST) trial (https://masttrial.org) aims to clarify the length of most beneficial anti-epileptic treatment based on amount of further seizures and to evaluate phenytoin and levetiracetam as well as to answer if one week therapy of phenytoin and levetiracetam should be admitted in order to prevent seizures (Clarkson & Ahmed, 2022).

7.1.6 Osmotic therapy

Cerebral edema control involves infusions of hyperosmotic agents, such as mannitol and hypertonic saline. Hyperosmotic treatment is especially indicated in NICU for acute rises in ICP for its rapid effect. Concentrations of hypertonic saline range between 1.7% and 29.2%. However, studies have not been able to provide evidence indicating the most favorable agent and when and if it should be administered in order to reduce increased ICP. Hypertonic saline decreases cerebral edema by removing water from the cells, leading to decrease in parenchymal tissue pressure, which further reduces ICP. (Helmy et al., 2007). Recent meta-analyses prefer hypertonic saline over mannitol in management of ICP, for it increases intravascular volume and is not associated with consequent diuresis and associated with renal toxicity, which may result in hypovolemia and hypotension (Kamel et al., 2011; Li et al., 2015). It is also recognized, that there is no advantage from prophylactic hyperosmotic therapies in order to prevent increased post-traumatic ICP in TBI (Menon & Ercole, 2017). Recent The Continuous Hyperosmolar Therapy for Traumatic Brain-Injured Patiens (COBI)-RCT showed that early continuous hyperosmolar therapy did not lead to better outcomes at six months (Roquilly et al., 2021). However, the latest BTF guidelines suggest that increased ICP can be effectively lowered with mannitol therapy at doses of 0.25 to 1 gram per kilogram body weight and simultaneously arterial hypotension should be avoided (Carney et al., 2017).

7.1.7 Routine ICU interventions

TBI patients admitted to NICU need routine ICU interventions besides TBI targeted therapies. Recent BTF guidelines recommend early nutritional support aiming to fulfill nutritional requirements as soon as patient is haemodynamically stable. Cochrane review has shown evidence that early feeding might lead to improved outcomes and early intensive nutritional support improves immunologic function of the patient following TBI (Helmy et al., 2007). Peptic ulcer prophylaxis is indicated, for sTBI is a known risk factor for stress ulcers (Helmy et al., 2007). Coagulopathy and venous thromboembolic disease are common findings in patients with TBI. While blood component transfusions are commonly used to treat coagulopathy, there is growing interest for usage of factor concentrates, such as tranexamic acid (TXA) and desmopressin (Menon & Ercole, 2017) Guidelines suggest that LMWH or low-dose unfractioned heparin may be used together with mechanical prophylaxis.Yet, it increases the risk for augmentation of intracranial hemorrhage (Carney et al., 2017). Cerebral edema may arise by imbalance of salt and water. Hyperosmotic therapy or diabetes insipidus may lead to

hypernatreamia and hyponatremia may occur due to SIADH or incorrect hypotonic therapy. Current therapies aim to correct these imbalances (Menon & Ercole, 2017.). According to recent BTF guideline, steroids should not be used for lowering ICP or to improve patient's outcome (Carney et al., 2017). Drainage of CSF via EVD is recommended to reduce ICP during the first 12 post-injury hours, when the patient's initial GCS is <6 (Carney et al., 2017). According to protocol, this measure should be utilized at stage 2 (Menon & Ercole, 2017).

7.2 Second-line strategies

If patient's ICP remains increased despite of standard medical treatments, other available and potentially harmful strategies should be considered as options. These include brief periods of hyperventilation for decreasing intractable ICP. Delayed induced hypothermia is also used as a second-line strategy to treat increased and uncontrollable ICP and research have shown evidence of 40% reduction of ICP and a notable decrease in mortality and severe disability at six months (Helmy et al., 2007). However, as already discussed in Chapter 5.11, hypothermia should only be induced when only very few alternatives remain, and not as a prophylactic measure. The last rescue therapy for medical management of uncontrollable ICP can be done using metabolic suppression through profound sedation. Barbiturates are commonly used for this therapy, but they have drawbacks, such as hypotension, haemodynamic instability, complications of respiratory system, loss of potassium, as well as impairment of kidney and liver function. Nevertheless, use of barbiturates should only be used as rescue treatment when ICP remain refractory (Menon & Ercole, 2017). Secondary DC is used as a second-line rescue therapy for saving lives and it is widely discussed in the next chapter.

8. Decompressive craniectomy

8.1 Definition & purpose

DC is a neurosurgical procedure involving removal of part of the skull in order to decrease elevated ICP. Increased ICP can result from cerebral edema or mass lesions, but DC effectively creates additional space for the swollen brain, with the aim of reducing ICP. DC can be carried out as a primary or secondary procedure. Primary DC is commonly conducted after the evacuation of an acute subdural hematoma (ASDH). Conversely, secondary DC is typically last-tier intervention in a patient with sTBI and increased ICP, which remains refractory after escalated ICP reducing interventions (Smith, 2017).

8.2 Indications for DC

Performing secondary DC is indicated in case of severe intractable ICP after failed maximal medical therapy, when previous tiered treatments for intracranial hypertension have failed (Smith, 2017). These tiered treatments include elevation of head of the bed, ventilation, sedation, fluid management, seizure treatment, neuromuscular blockade, administering of hyperosmolar agents, normothermia, CSF drainage through EVD, induced hypertension, therapeutic hypothermia and barbiturates (Smith, 2017). More rarely, DC has been used as a second-tier therapy to control mild intracranial hypertension, but recent RCT have shown evidence against this treatment as second-tier therapy (Stocchetti et al., 2017)

8.3 Types

Secondary DC can be undertaken through three main approaches: bifrontal craniectomy, unilateral hemicraniectomy and bilateral hemicraniectomy. During the first, skull flaps of frontal bone from both sides of the forehead are removed enabling decompression of the frontal lobes of the brain. In unilateral hemicraniectomy, only one hemisphere of the skull is removed. This is typically performed on the side of the brain presenting the most pronounced swelling or injury. Bilateral hemicraniectomy is a procedure, where parts of the skull are removed from both hemispheres to provide more extensive decompression of brain parenchyma (Smith, 2017).

8.4 Outcomes & complications

Outcomes after DC have been under wide research through past years. Recent consensus is that following TBI, DC might lead to reduced mortality compared to medical therapy, but to increase in severe disability (Smith, 2017). However, recent results at 24 months of Randomized Evaluation of Surgery With Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp) trial showed that patients who underwent surgical procedure improved more over time (Kolias et al., 2022). These results based on previous RCTs are discussed in the next section. DC is associated with several possible complications after the procedure. These include, for example, contusions, contralateral mass lesions and hydrocephalus. Skull reconstruction (i.e. cranioplasty) is commonly conducted a few months after DC and it may lead to it's own complications such as infection and problems with wound-healing as well as seizures, intracranial haemorrhage and brain swelling. Although patients who have undergone DC face complications and a significant rate of disability and depression, a recent systematic review provided evidence of nearly 75% of satisfaction rate from patients and their caregivers when asked about experiences in DC (Kolias et al., 2013).

8.5 Previous trials

Three main multicenter RCTs have been carried out in the field of DC following TBI: Decompressive Craniectomy (DECRA), RESCUEicp and Randomized Evaluation of Surgery with Craniectomy for patients Undergoing Evacuation of Acute Subdural Haematoma (RESCUE-ASDH).

8.5.1 The DECRA trial

In the DECRA study, 155 adults with diffuse sTBI were randomly assigned either to undergo bifrontal decompressive craniectomy or to receive standard therapy when encountering refractory intracranial hypertension (defined as ICP over 20 mm Hg for over fifteen minutes in a one hour period) within the first 72 hours postinjury (Cooper et al., 2011). Main focus was to evaluate the extended Glasgow Outcome Scale (GOSE) score after six months. DC was associated with lower ICP than in medical therapy group, fewer hours of ICP over 20 mmHg and shorter stay in ICU. Mortality rates were similar in both groups (19% and 18%), but surgical group was identified with poorer GOSE (70% vs 51%; $p = 0.02$). Following post hoc analysis revealed that the rate of unfavorable outcomes was no longer significant after pupil reactivity was adjusted at baseline (Cooper et al., 2011; Kolias et al., 2013). Findings from the DECRA trial indicate that DC is not to be used as a neuroprotective measure for addressing moderate posttraumatic intracranial hypertension (Smith, 2017).

8.5.2 The RESCUEicp trial

The RESCUEicp trial enrolled 408 patients between the ages of 10 and 65, all of whom had severe and refractory posttraumatic intracranial hypertension despite receiving protocol-based medical management. Patients were considered eligible for randomization, either to DC group or to medical treatment group, following trauma whether their ICP remained consistently above 25 mmHg for at least one hour and showed no response to initial and secondary ICP-reducing interventions. This study used also GOSE score as a primary endpoint and these scores were evaluated at 6, 12 and 24 months. Results of this study were published in 2016, stating that DC led in significantly reduced mortality (26.9% vs 48.9%) but increased rates of vegetative state (8.5% vs 2.1%), reduced severe disability (21.9% vs 14.4%), and upper severe disability (independent at home; 15.4% vs 8%) than medical treatment. Additionally, 45.4% of surgical patients had a favorable outcome compared to 32.4% in the medical treatment group ($p = 0.01$) when evaluated at 6 and 12 months. When evaluated at 24 months, for every 100 patients treated surgically, 21 additional patients survived compared to medical group (Hutchinson & Kolias, 2016; Kolias et al., 2022). These results emphasize the benefit of secondary DC as a life-saving procedure to lower mortality in intractable intracranial hypertension following sTBI (Smith, 2017), (Kolias et al., 2022).

To conclude, results of these above-mentioned studies suggest that bifrontal DC should not be concerned as a neuroprotective treatment in the case of mild or moderate intracranial hypertension (Cooper et al., 2011). Secondary bifrontal or unilateral DC are considered as last-tier therapies to lower mortality in patients with refractory intracranial hypertension (Hutchinson & Kolias, 2016). Lastly, surgical patients undergoing DC show improvement with time which supports longer follow-up times in clinical trials (Kolias et al., 2022).

8.5.3 The RESCUE-ASDH trial

ASDH is a critical condition within patients with TBI and it is noticed to correlate with high mortality and low rates of functional recovery. It is reported that two out of three of TBI patients undergoing neurosurgical surgery in the emergency settings have an ASDH evacuated (Kolias et al., 2022). Additionally, these patients often have parenchymal injuries and swelling of the brain. In RESCUE-ASDH-trial, patients were randomized intraoperatively to receive either DC or craniotomy, a surgical procedure where bone flap is replaced after the surgery. This clinical trial compared the effectiveness of primary DC versus craniotomy and bone-flap replacement after evacuation of an ASDH following head trauma. Results of this study state that disability as well as quality-of-life outcomes did not differ between groups. Additional surgery was performed more frequently in the group who underwent craniotomy,but craniectomy led to additional wound complications (Hutchinson et al., 2023).

9. Discussion and future challenges

Neuromonitoring of TBI currently relies on threshold-based “reactive” model, in which single parameters are monitored and, therefore, treated. This “one size fits all” approach is rather outdated. These parameters should be monitored by using MMM, combination of monitor techniques and clinical data that provide immediate information about the ongoing brain function and possible secondary injuries. Thus, the modern MMM consists of simultaneous recordings of various discussed parameters in this thesis is more trend-based, rather than threshold-based. Clinicians need to understand the changes of different trends and to make timely decisions as a result of integrative

approach of different parameters besides the clinical skills (Le oux, 2013). MMM concept is not yet well applied to routine use in NICU globally and only low levels of evidence exist regarding beneficial combining of monitoring methods. Thus, more studies about the utility of different modern monitoring tools are needed to be conducted to ensure the impact on the clinical practice and outcome of patients. In addition, as mentioned earlier, these monitoring values should be used in integrated fashion, combined with other clinically meaningful findings and final decisions should be well discussed with the ICU team before any new interventions or procedures. ICP monitoring remains as the established gold standard in monitoring of TBI patients. MMM approaches using PbtO2 and/or CMD are increasingly being applied into clinical use. Non-invasive methods for monitoring ICP, such as ONSD measurement with ultrasonagraphy, NIRS and TCD have shown promise and hold potential as alternatives to conventional invasive approaches, more specifically, in low resource settings.

Blood-based biomarkers have been the subject of extensive research, however, still there is no clinically validated biomarker for the day to day use in the ICU for monitoring the secondary injuries following TBI. For establishing stronger evidence for the clinical applications for the promising biomarkers, for example, S100B, GFAP and NF-L, collaborative research having harmonized methodology is needed, especially considering longitudinal sampling instead of single sampling points (Posti & Tenovuo, 2022). There is also demand for a new generation of TBI biomarkers ,including different omics, to provide individualized treatment and to develop precise prediction models. The underlying biological processes behind TBI are still not yet well understood and omics technologies could have potential to provide advancements in this area in the coming years. In addition, machine learning approaches and artificial intelligence (AI) may ease the interpretation of MMM in the future (Lindblad et al., 2022) and the application of AI could improve the accuracy of treatment in the neurointensive care of TBI patients. (Kim et al., 2024).

Latest widely recognized conclusions from recent studies suggests that secondary DC could be applied in the treatment of post-TBI intracranial hypertension, but it could lead to permanent harm, causing, for example, severe disability. Hence, the decision to apply DC as last-tier management of sTBI should be considered thoroughly, and whenever possible, with relatives of the patient.

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