Treating Intracranial Hypertension in Patients with Severe Traumatic Brain Injury during Neurointensive Care

New Features of Old Problems?

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Abstract

Despite the envisioned breakthrough prophesied for the end of the past century in healing brain injured patients, both clinicians and basic scientists are still struggling with this burden. In the past decades, intensive research has brought forward a plethora of different targets which – in part – have already been integrated in clinical routine directed at detailed monitoring, therapeutic interventions, and prevention of secondary deterioration. While intracellular targets remain obscure alterations on a larger scale as e.g., measured intracranial pressure (ICP), calculated cerebral perfusion pressure (CPP), and various imaging techniques are fundamental components of our present clinical understanding. At bedside, comprehension of pathophysiological loops and circuits of a given value (e.g., ICP) depends on individual knowledge, interpretation, and availability of additional diagnostic steps. As stated in the guidelines brought forward by the American Association of Neurological Surgeons and evaluated in various reports by the Cochrane Library we are still lacking prospective, randomized trials for the majority of the proposed diagnostic and therapeutic interventions. In this context, a recent meta-analysis even questioned the importance of ICP monitoring as we are lacking data from randomized controlled trials clarifying the role of ICP monitoring. The present review is to give an overview of various diagnostic and therapeutic possibilities based on reports published in the past 5 years to strengthen current approaches and nourish future well-designed investigations how to avoid and treat intracranial hypertension.

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Key Words

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Introduction

The most feared complication following severe traumatic brain injury (TBI) is an increase in intracranial pressure (ICP) which may also become therapy-refractory making ensuing death inevitable. Elevated ICP as measured continuously is a number which requires thorough and differentiated analysis of various possible reasons (Figure 1). In this context, the time point of intracranial hypertension is crucial: during the early phase (minutes/hours to initial 2–3 days), new onset or significant progression of hemorrhages and edema are the most common reasons [1]. Developing intracranial hypertension at later time points which is not observed under standard experimental conditions can be caused by progressing perifocal and generalized edema formation and disturbed vascular responsiveness. Overall, compression and edema form a vicious circle with various potential therapeutic targets (Figure 2). In this context, the heterogeneity of TBI with its different lesions might require lesion-dependent interventions. The easiest treatment step is the surgical removal of space-occupying lesions compressing the brain (subdural and epidural hematoma [SDH, EDH]) providing their speed of development has not surpassed the time point of salvageable iatrogenic intervention. More complicated to

treat and correct are different changes developing in parallel and sequentially which can induce or aggravate underlying damage over time. Despite the intense research and the promising results obtained by specifically modulating identified cellular targets in "non-intensive care unit (ICU) rodents" [2], the equally successful implementation of these laboratory results in ICU patients with severe TBI has failed. Just recently, the Dexanabinol trial which had been envisioned to provide an effective therapy by inhibiting cellular damage mediated by reactive oxygen species, glutamate and tumor necrosis factor was announced a failure. Consequently, we are left with our basic treatment possibilities.

In this review, the authors have tried to address the old issues and questions on how to treat intracranial hypertension, focusing on findings published in the past 5 years.

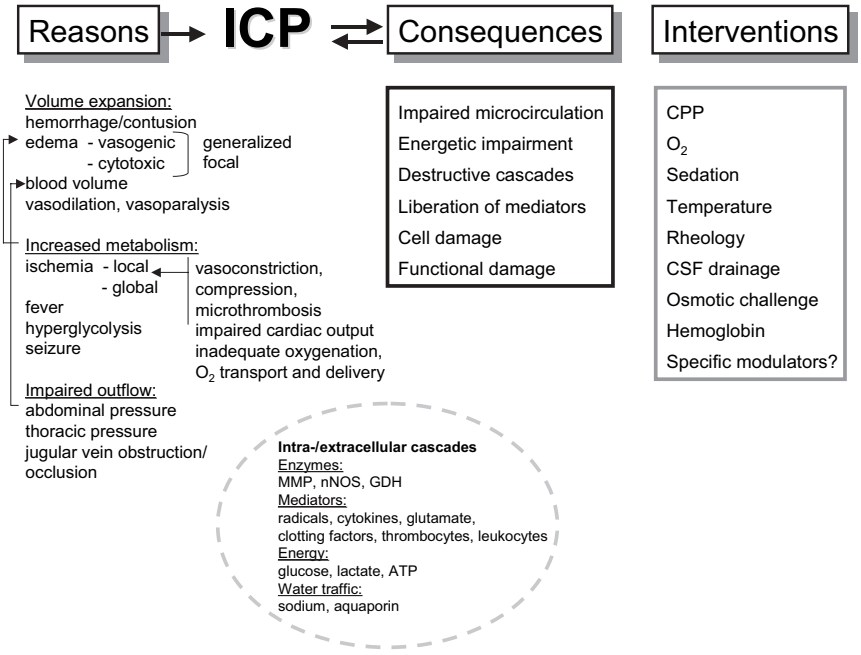

Figure 1. Schematic drawing showing possible pathophysiological circuits which contribute to intracranial hypertension following severe TBI which, in turn, can activate or aggravate underlying pathologic changes. Corrective interventions are limited.

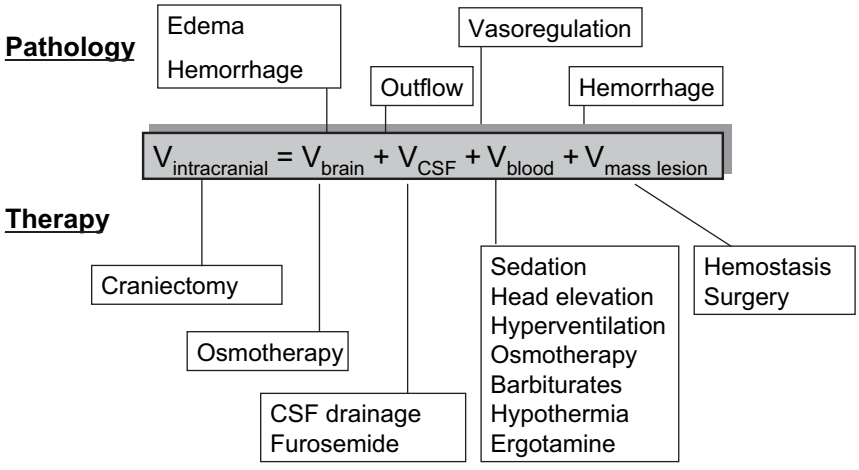

Figure 2. The intracranial volume is influenced by different compartimentalized components which, however, influence each other. To a certain extent these components are individual therapeutic targets. However, it is important to understand that aggressive treatment of one component might induce adverse and deleterious effects in a different part owing to the tight functional dependencies.

Identification of Secondary Injury and Deterioration

Both, clinical and experimental research strongly support the perception that reliable and easy-to-perform monitoring techniques and methods are indispensable to unmask further deterioration and to also initiate and guide specific therapeutic and pharmacological interventions. For this, measuring changes in ICP is the most efficient basic monitoring method to reveal pathologic alterations within the intracranial compartment which is complemented by additional monitoring approaches. ICP values as such are nonspecific as they cannot differentiate the actual cause for the observed increase in ICP (Figure 1). Nevertheless, ICP monitoring is crucial in prompting diagnostic steps and guiding therapeutic interventions.

Overall, secondary injury is characterized by its dynamic development initiated by the primary injury. In this context, speed, duration, and extent of injury progression are variable in time and location and appear to be different for structural and functional damage. Progression and new onset of structural lesions occur pre-

dominantly within the first 24–72 h. Edema formation develops in parallel but persists longer than hemorrhages which show signs of resolution within 5 days. Consequently, the initial hours to days are the most crucial phase requiring intensive monitoring to identify secondary deterioration. Nevertheless, the subsequent days to weeks are overshadowed by potential secondary insults related to focal or diffuse ischemia, persistingly open blood-brain barrier, the inflammatory response, infections, and other organ complications which have been shown to influence morbidity and mortality [3].

Since revelation of functional deterioration is the key in improving our current therapy, the following section summarizes the different monitoring techniques which are used to assess development, extent, and regression of various causes of elevated ICP.

Brain Imaging

While the readily available CT (computed tomography) analysis is an integral and widely employed part in evaluating presence, severity, and development of structural intracranial pathologies, it does not reflect new onset or progression of functional deterioration. Other imaging techniques known to disguise functional changes (PET [positron emission tomography], SPECT [single-photon emission computed tomography], H-MRS [proton magnetic resonance spectroscopy], MRI [magnetic resonance imaging]) are not readily available, difficult to conduct in cardiopulmonary and hemodynamically unstable patients, can only be performed discontinuously, are still academic in nature, and have not been integrated in the actual clinical management. Assessment of functional disturbances is crucial to induce and adapt therapeutic interventions. In the classic ICU setting with sedated and mechanically ventilated patients "functional disturbance" refers to changes on the cellular level which involves not only neurons but also astrocytes and endothelial cells. In this context, it is important to comprehend that actual cell-based alterations are highly dynamic processes which influence each other in a heterogeneous spatial and temporal manner.

Present conclusions. In daily routine CT analysis is the mainstay within the diagnostic and therapeutic decision-making. During the acute phase only MRI studies with their logistic and patient-dependent difficulties are justified to determine brain stem lesion which otherwise are not visible on CT scans. Assessing functional alterations by MRI and PET requires an active and cooperative patient and, thus, is of inferior assistance in comatose and sedated patients.

Intracranial Pressure (ICP) and Compliance

The hallmark of posttraumatic structural and functional disturbance is an elevation in ICP due to increased intracranial volume related to expanding hemorrhages (EDH, SDH, contusions) and/or accumulation of water within the extracellular and intracellular compartment, known as vasogenic and cytotoxic edema. Furthermore, insufficient as well as sustained cerebral perfusion (hyperemia) due to ischemia and increased intracranial blood volume, respectively, can induce intracranial hypertension [4, 5]. For this, introduction of ICP monitoring devices within the subdural space, brain parenchyma and ventricular system are integrated in the routine treatment of these patients. As evaluated within the guidelines brought forward by the American Association of Neurological Surgeons (AANS; *www2.braintrauma.org/guidelines/downloads/btf_guidelines_management.pdf*) subarachnoid, subdural, and epidural monitors are less accurate compared to parenchymal and ventricular ICP probes. In this context, it is important to comprehend that the suggested ICP threshold of 15 mmHg is based on supratentorial measurements, as patients can also herniate with normal values, if the expanding lesion is located in close proximity of the brain stem. In general, ICP values > 15 mmHg reflect underlying pathology and any increase exceeding 25 mmHg should prompt further diagnostic evaluation (see AANS guidelines).

Determination of intracranial compliance as a measure of increased stiffness of the brain by infusing fixed amounts of fluid in the ventricular system is thought to unmask a pathologic pressure-volume relationship and to also predict forthcoming hypertension when small increases in volume induce a larger than normal increase in pressure under conditions of exploited compensatory mechanisms as seen in cases of space-occupying lesions. As a function of elevated ICP the tolerable amount of injectable volume into the ventricular system decreases significantly, as ICP exceeds 20 mmHg, irrespective of age [6]. However, given a low incidence of episodes identified to adequately predict pathologically elevated ICP, i.e., 16% of 225 episodes determined in ten patients suffering from severe TBI, this technique requires further modification before it can be introduced in the clinical routine as an early warning system for ensuing deterioration [6].

Present conclusions. Measuring ICP is the crucial and central monitoring parameter for any physician treating patients with TBI. Changes in ICP need to prompt more in-depth diagnosis to determine the cause for intracranial hypertension, thereby allowing more specific treatment, and to prevent uncontrollable decompensation. Assessing ICP automatically provides information about global cerebral perfusion, as the cerebral perfusion pressure (CPP) results from ICP and mean arterial blood pressure (MABP). Translation of bedside analysis of disturbed intracranial compliance to daily routine has not been completed due to technical limitations.

Electrophysiological Investigations (EEG, EPs)

Disturbances in neuronal activity and axonal conductance can be assessed by electroencephalography (EEG) and evoked potentials (EPs) which can determine the site of functional impairment and even allow prognostic statements [7]. Cortical responsiveness to exteroceptive tactile, acoustic, and noxious stimuli requires intact transmission from the periphery to central areas (sensory stimulation) with adequate processing in the gray matter. On a cellular level, excitatory and inhibitory inputs require viable and metabolically active neurons and astrocytes to generate and modulate electrogenic potentials arising from cortical and subcortical structures. Any disturbance due to structural lesions within the white or gray matter of brain and spine or functional impairment related to hypothermia and administered sedative drugs can hamper the reliability of these investigations. Nevertheless, these techniques allow insight into pathologic alterations which in conjunction with metabolic analysis might unmask severity of injury and pharmacological reversibility as suggested by the findings of Vespa et al. who were able to reveal nonconvulsive status epilepticus which otherwise had gone undetected [8]. Consequently, specialists recommend continuous EEG monitoring during the initial 48 h [9].

Present conclusions. EEG analysis remains a controversial area due to its physiological, pathophysiological and technical complexity, since we can neither determine the actual anatomic depth at which changes are induced nor assess the extent of neuronal and glial imbalance. More refined and simplified approaches as e.g., the BIS (bispectral index) EEG might reveal neuronal stability or instability continuously at bedside, possibly helping to disguise neuronal from glial activity, whenever surrogate markers as e.g., decreased jugular venous oxygen saturation ($SjvO_2$) occur in face of decreased EEG (neuronal) activity. EPs are helpful in assessing brain stem lesions, thereby aiding the complex decision process.

Microdialysis

Recent introduction of microdialysis in the clinical routine has opened the possibility to unmask otherwise occult pathologic metabolic alterations based on routine analysis of glutamate, glucose, lactate, pyruvate, and glycerol [10], and calculated indices. In addition, pharmacokinetic studies can be performed [11]. A large number of reports have convincingly demonstrated its applicability and usefulness in assessing cellular impairment following TBI, providing certain limitations are considered. The low spatial and temporal resolution dictated by the position and speed of dialysis, respectively [12], do not allow to transfer these local alterations to distant areas and might not be able to reveal ensuing changes early enough to allow preemptive interventions. In addition, recovery rate is not routinely determined under in vivo conditions by injecting a metabolically inert substance via a second microdialysis catheter inserted in close proximity [13]. Furthermore, we cannot correct for concentration or dilution effects due to edema-related shrinkage or expansion of the extracellular space and we are not able to exclude diffusion handicap caused by activated glia surrounding the catheter over time.

Present conclusions. Cerebral microdialysis disguises local pathologic processes as well as pharmacodynamic effects. Whether the latency of these changes might be overcome by a higher sampling rate (1- to 5-min intervals vs. routine 30-min intervals) which increases the logistical and personal workload remains unclear. In this context, a sophisticated automated artifact recognition tool becomes indispensable. The associated costs limit its general integration.

Cerebrospinal Fluid (CSF) Analysis

In patients with noncompressed lateral ventricles, ventricular catheters are inserted to lower ICP by draining CSF. This approach can also be used to determine metabolic and immunologic changes [14] in CSF to unmask underlying pathologic changes. This technique, however, is compromised by certain methodological pitfalls. For one, drained CSF reflects global changes and mea-

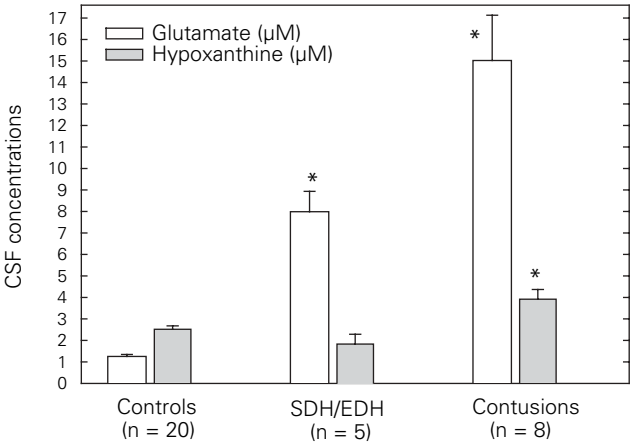

Figure 3. Influence of different traumatic brain lesions on CSF glutamate and hypoxanthine concentrations, reflecting underlying excitotoxicity and energetic impairment. Highest levels were observed in patients presenting with contusions (*p < 0.05 vs. controls).

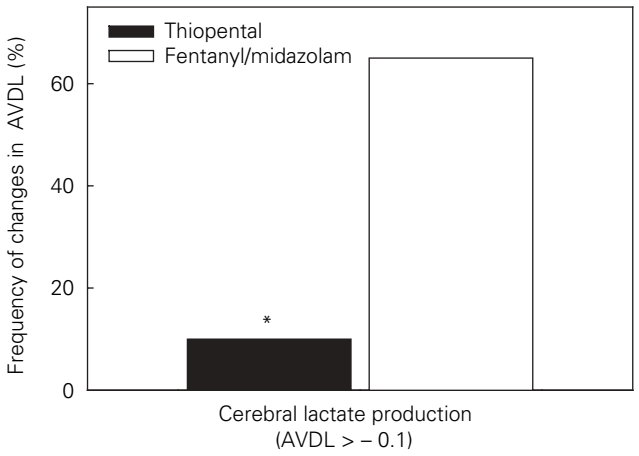

Figure 4. In patients with therapy-refractory intracranial hypertension, administration of high-dose thiopental significantly reduced the frequency of metabolic compromising events reflected by a decreased number of pathologically elevated jugular venous lactate (negative arterio-jugular venous difference) compared to patients treated with fentanyl and midazolam (*p < 0.001).

sured solutes are strongly influenced by intracisternal blood, the bulk flow toward the ventricular system washing these substances out of the brain, and the speed and amount of produced and resorbed CSF which might change over time and is not quantified under clinical conditions. Furthermore, there is no clear consensus whether single or repetitive measurements are required or if CSF needs to be collected continuously. The fact that ventricular catheters cannot be inserted in patients with narrow or compressed lateral ventricles or CSF cannot be drained due to progressive edema-related compression of the ventricular system implies that only patients with brain injuries of a presumably lesser extent or a more complicated secondary development are investigated. This, in turn, does not allow to extrapolate the determined changes to all patients. Nevertheless, this technique allows to assess the impact of underlying type of brain lesions and can also be used for pharmacodynamic and pharmacokinetic studies. In this context, highest glutamate and hypoxanthine concentrations were determined in patients with contusions and mixed lesions compared to control patients (lumbar CSF) and patients with isolated SDH or EDH (Figure 3). Inducing a burst suppression pattern by the administration of thiopental resulted in a significant decrease in CSF glutamate, lactate and hypoxanthine concentrations [15].

Present conclusions. CSF analysis remains a simple monitoring approach which, however, is limited to patients with less or more severe injuries, depending on the size of the ventricular system. The fear for ventriculostomy-related infections might restrain this approach.

Jugular Bulb Catheter

Retrograde insertion of a special catheter in the internal jugular vein allows to continuously determine changes in $SjvO_2$ [16] and discontinuously measure arterio-jugular venous differences of humoral and cellular components leaving or entering the brain [17–20]. This monitoring approach reflects global alterations and is routinely used to guide and control hyperventilation to reduce elevated ICP. This allows to detemine hyperventilation-induced vasoconstriction and prevent injury-aggravating ischemia [21]. As any attempt to study metabolic and thus functional alterations, concomitant drug administration needs to be considered, as pharmacodynamic influences may supervene. In this context, we have observed a significant reduction in lactate production reflected by the lower frequency of negative arterio-jugular venous lactate differences in patients subjected to high-dose barbiturate coma compared to patients receiving benzodiazepines and opioids (Figure 4).

Different $SjvO_2$ values were identified to have a therapy-guiding potential: while $SjvO_2$ values < 50% reflect ischemia, levels between 50 and 65% could reveal impending ischemia, and $SjvO_2$ between 65 and 75% are considered normal; levels > 76% reflect hyperemia or

vast depression of metabolism characteristic of severe injuries. Most frequent causes for pathologically decreased $SjvO_2$ values are hyperventilation, hypovolemia, and anemia which can be prevented or corrected, thereby reducing incidence of intracranial hypertension and improving outcome [1].

Present conclusions. Retrograde cannulation of the internal jugular bulb to monitor cerebral alterations is technically easy but is limited by the frequency of analysis and the declining data quality within several days following insertion of the fiber-optic catheter. Measuring arterio-jugular venous differences might complement multimodal monitoring especially in regard to systemic influences related to diseases known to develop over time in critically ill patients (e.g., organ dysfunction, infections, sepsis, etc.). With this approach more patients could be monitored especially if penetrating probes (microdialysis, tissue probes) cannot be introduced.

Brain Tissue Oxygenation

Following TBI, the injured brain is in a state of distress characterized by sustained vulnerability owing, among other reasons, to its limited energetic reserves in face of sustained and dysregulated excitation. Consequently, the brain requires sufficient oxygen to prevent additional cell damage from impaired oxidative metabolism necessary to meet activation-induced increases in energy demands. Changes in tissue pO_2 ($ptiO_2$) reliably reveal evolving tissue perturbation. Detrimental $ptiO_2$ threshold below which ischemic damage develops and which is associated with pathologic neurochemical alterations [22] and a worse outcome is 8–10 mmHg [23, 24]. Changes in $ptiO_2$ can also serve to discriminate anaerobic from nonoxidative metabolism, as an increase in extracellular lactate can also be caused by sustained activity and adapted lactate utilization in face of adequate perfusion and supply with oxygen and nutrients. Similar to the $SjvO_2$, local $ptiO_2$ changes can be used to assess limits of hyperventilation and thus guide this therapeutic intervention [25]. This technique with its monitoring confined to a small area of interest at the cortical-subcortical junction within the frontal cortex of the uninjured or lesser injured hemisphere faces similar methodological limitations as the biochemical monitoring via microdialysis. This cannot be overcome by its high temporal resolution with a sampling rate of 1–10 recordings/min.

Present conclusions. As seen with microdialysis, $ptiO_2$ recordings require insertion of penetrating probes which might not be feasible in patients with bifrontal lesions. Due to the high frequency of data recording a sophisticated artifact recognition software is indispensable to guarantee reliable interpretation of the collected data. The long "calibration" of up to 6 h limits its usefulness during the early period following probe placement.

Cerebral Perfusion

Ever since its initial description by Graham et al. in 1978 [26] reporting ischemic damage in 91% of patients succumbing to their nonmissile head injuries, diagnosis, avoidance, and treatment of impaired perfusion following severe TBI have prompted a multitude of clinical and experimental studies. The easiest but also most crude assessment of cerebral perfusion is to calculate the difference between MABP and ICP. This number, however, does not reflect regional alterations which are known to be extremely heterogeneous. Assessing cerebral perfusion can be performed invasively and noninvasively. As recently and convincingly shown by Vajkoczy et al. [27], insertion of a special thermodilution probe allows to continuously and reliably determine changes in cerebral perfusion as evaluated by simultaneous stable xenon-enhanced computerized tomography scanning (sXe-rCBF) which contrary to the laser Doppler methods reveals absolute flow values [ml/100 g/min]. In a small series of patients, Jaeger et al. [28] could show that this technique allows to detect impaired perfusion judged by the changes in $ptiO_2$. Unfortunately, as other catheters used to aid neurointensive care, this probe "only" reveals local alterations. Assessing global changes in cerebral blood flow (CBF) at bedside using the transcranial thermo-dye-dilution technique, however, has yielded uncertain results compared to xenon-CT measurements [29].

Noninvasive bedside transcranial Doppler evaluation does not only reveal changes in blood flow velocity of the extra- and intracranial vessels but may also reflect microcirculatory impairment following TBI, as the low flow velocity which was reported to be most prominent ipsilateral to a focal pathology is associated with decreased $ptiO_2$, especially within the first days following injury [30]. This technique is performed discontinuously but with a higher frequency compared to imaging studies.

Imaging studies with their high spatial resolution are limited by the fact that these discontinuously performed and logistically challenging studies can only provide "snapshot" views. Perfusion CT [31], SPECT [32], PET [21], perfusion-weighted MRI [33], and xenon-CT [29] can reveal localization and extent of underlying impaired perfusion and ischemia and even unmask basal ganglia hypoperfusion.

Apart from identifying ischemia, assessing changes in perfusion is essential to determine if increased CBF exceeding the metabolic demand reflects hyperemia. This could result from sustained brain damage or an increased pressure load due to impaired autoregulation which could be reduced by lowering CPP.

Present conclusions. Although decreased as well as increased cerebral perfusion are the most crucial pathophysiological changes accounting for secondary damage, routine surveillance of disturbed perfusion is predominantly based on surrogate markers ($ptiO_2$, $SjvO_2$, metabolic changes). More widespread application of bedside continuous approaches combining regional and global perfusion is important to improve both understanding and therapeutic guidance. This will automatically facilitate interpretation of other monitoring parameters, and thereby either initiate or stop therapeutic interventions.

Proteomics

Due to its recent commercial availability, analysis of various proteins determined in microdialysis or CSF samples can be used to investigate changes of extracellular and even intracellular proteins following their release or liberation. This approach might allow to identify proteins which might be useful predictors for disease characteristics following TBI as seen after stroke [34].

Present conclusions. More data is needed before a meaningful conclusion may be drawn.

Cerebral Monitoring: Is it Local Versus Global or a Combination of Both?

Successful development and feasible transfer from bench to bedside have facilitated the integration of various monitoring techniques in the daily routine support and care of patients with severe TBI. Nevertheless, as with any – especially novel – "experimental" diagnostic approach certain limitations inherent to the applied techniques and methods can make the clinical decision process more difficult, as differentiated interpretation of collected data might not reveal pathologic alterations at the time point of evaluation but may only become obvious following post hoc analysis. Insertion of special catheters despite their small diameters (ICP probe: 1 mm; $ptiO_2$: 0.8 mm; microdialysis: 0.8 mm; thermodilution probe: 1 mm) carries a risk of additional damage, mainly hemorrhage especially in preinjured regions. Thus, these catheters should only be inserted within the frontal cortex to avoid any damage to the primary and secondary sensory and motor fields located more posterior.

While these catheters are generally assumed to only reflect local changes confined to a small volume surrounding these probes – used to argue against their usefulness –, this must be challenged by the fact that this assumption might only hold true at low ICP levels and maybe also in craniectomized patients. Under experimental [35] and clinical [36] conditions the rigid skull will translate increased pressure caused by a focal or hemispheric lesion to the contralateral hemisphere and also to other regions within the ipsilateral hemisphere over time as the existing pathology extends. Consequently, monitoring the contralateral or lesser injured hemisphere will reveal serious and relevant alterations reflecting severity and extent of underlying disturbance. This, in turn, implies that whenever pathologic alterations occur in the contralateral hemisphere, functional integrity of the entire brain needs to be considered at stake. The initial conception that metabolic abnormalities are restricted to superficial regions has been recently questioned, as a significant reduction in metabolic oxygen rate was also observed in subcortical white matter remote from focal hemorrhagic lesions, suggesting more diffuse injuries [37]. However, the studied patients were heterogeneous in terms of injury severity, considered time points, and administered drugs.

The strong need to closely monitor patients with severe TBI and to start as early as possible to avoid missing preventable insults which increase morbidity and mortality has become self-understood. This is strengthened by retrospective reports showing a significant reduction in mortality, increase in functional outcome, shortened hospitalization, and reduction in costs [38–40]. Nevertheless, critics still question the need for intensified monitoring, as the efficacy of ICP and multimodal monitoring has never been studied in a prospective, randomized clinical trial [41]. Overall, there is a growing body of evidence showing that these

monitoring techniques and methods integrated in the neurointensive care setting to date can detect deterioration, guide therapeutic and pharmacological interventions, and thereby contribute to the improvement of these patients. Thus, designing a randomized trial assigning patients to a nonmonitoring arm would be unethical and therefore inapplicable. However, the extent and frequency of monitoring could be subjected to a randomized trial. Furthermore, the length of monitoring required to guarantee a more favorable outcome still remains under debate. While some centers discontinue monitoring and sedation after a few days, other centers maintain monitoring and sedation until ICP remains stable without exceeding 20 mmHg. Based on our own experience, ICP can steadily increase during the first week, surpass 15 mmHg during the second week and approach 20 mmHg by the end of the second week (Figure 5).

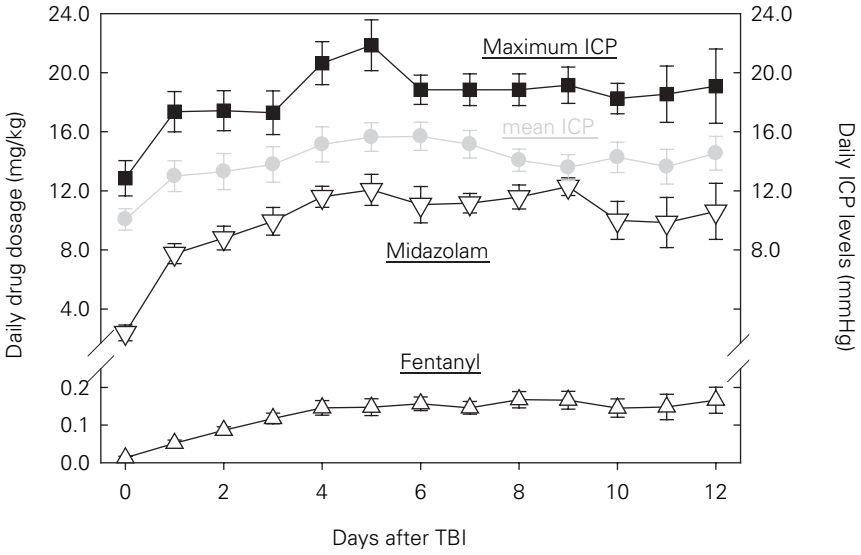

Figure 5. Temporal profile of changes in maximum and mean ICP determined in 16 representative patients suffering from severe TBI. ICP was significantly increased on the first posttraumatic day and after 1 week, remaining elevated thereafter. Within 4 days, fentanyl and midazolam were administered in their highest possible daily amount.
Under clinical conditions, infusion of fentanyl and midazolam followed the increases in ICP. Thus, it remains to be determined if a higher starting dose might attenuate subsequent intracranial hypertension.

Present conclusions. Further technical development and more widespread application of various monitoring techniques in primary and tertiary hospitals will generate more data and substantiate our knowledge which, in turn, will improve the overall treatment. It remains to be determined which parameters must be monitored and which are facultative to disguise evolving deterioration and improvement. In general, various parameters need to be combined to guarantee a holistic surveillance of local and systemic as well as cell-dependent changes. In addition, monitoring needs to be adapted to the temporal profile characterized by different influences and requirements.

Treatment of Secondary Injury and Deterioration

In principal, dictated by the progressive nature of evolving structural and functional deterioration our duty is to find ways and means to attenuate (= realistic goal) or even stop (= ideal situation) this development without endangering the patient. What is oversimplified by the dichotomy of e.g., ICP- versus CPP-targeted therapy is, in reality, much more complex. In fact, we might have to combine the AANS guidelines and the treatment strategies advocated by Grände et al. known as the "Lund concept" [42] in the same patient at different time points. The following part summarizes new knowledge and novel developments for the different treatment steps considered essential in the treatment of intracranial hypertension.

CPP- or ICP-Targeted Therapy – the All-Time Controversial Expanded by the Volume-Targeted Therapy ("Lund Concept")

Based on a multitude of publications using different methods to determine cerebral perfusion (PET, sXe-CT) posttraumatic brain ischemia strongly influences neurologic outcome. Consequently, maintenance of adequate cerebral perfusion is essential to avoid additional cell damage possibly aggravating underlying injury. In this context, adequacy of perfusion is difficult to define as it is subject to heterogeneous local and temporal changes with a strong interindividual variability [43], ranging from impaired perfusion [44] due to clotted or vasoconstricted or compressed vessels to increased perfusion (hyperemia) [43] caused by vasodilated or paralyzed vessels. If adequacy of perfusion is defined as sufficient metabolic support of neurons and glia, then metabolism-related parameters in addition to cerebral perfu-

sion must be continuously determined at bedside. This will allow us to respond to changes over time influenced by progression and resolution of hemorrhages and edema formation and also enable us to adequately react to iatrogenic manipulations and therapeutic interventions. Thus, aggressive therapeutic measures employed to influence cerebral perfusion without proper control might result in blood volume overload (hyperemia or flow-metabolism uncoupling) under conditions of endogeneously or pharmacologically depressed metabolic demand [43]. This, in turn, could induce aggravating elevated ICP. The initial CPP value of 70 mmHg set as the therapeutic goal by the AANS in 2000 was recently questioned and revised by the AANS in 2003 based on the observed volume- and pressor-induced increase in incidence of adult respiratory distress syndrome (ARDS) in patients who had been randomized to the CBF-targeted therapy [45]. As recently concluded by Juul et al., a CPP > 60 mmHg does not improve outcome providing ICP can be maintained < 20 mmHg [46]. Then again, others request to maintain CPP > 70 mmHg [47].

As clearly stated in the initial guideline, the AANS repeats that we are still faced with *"insufficient data to support treatment standards"* and suggests: *"Cerebral perfusion pressure (CPP) should be maintained at a minimum of 60 mmHg. In the absence of cerebral ischemia, aggressive attempts to maintain CPP above 70 mmHg with fluids and pressors should be avoided because of the risk of adult respiratory distress syndrome."* The crucial detail in guiding adequate cerebral perfusion is extensive monitoring. For this, we need to combine different approaches simultaneously, including focal and global assessment of metabolism and perfusion.

Contrary to the initial perception of a static ICP-CPP relationship, novel data show that the spatial and temporal heterogeneity in impaired perfusion, disturbed metabolism, and metabolism-flow mismatch reflect a more dynamic relationship which appears to be different for various lesions and could change over time within the same patient. Consequently, the optimal thresholds for ICP as well as CPP might not be isolated setpoints but could require more iatrogenic flexibility to adapt and guide therapeutic interventions by monitoring cerebral metabolism, allowing higher ICP values (> 20 mmHg) as long as an adequate perfusion threshold is maintained [48, 49]. Based on the calculated dynamic threshold levels for CPP and ICP, Chambers et al. could show that determined minimal CPP and maximal ICP values differ depending on extent/severity of underlying lesions [5]. Interestingly, minimum required CPP values were highest in patients with nonevacuated mass lesions (94 mmHg), possibly related to the concomitant compression of the microcirculation, requiring an increase in pressure gradient. An increase in CPP from approximately 70 to 90 mmHg appears necessary to reduce the ischemic brain volume, improve flow-metabolism coupling, decrease oxygen consumption, and increase $ptiO_2$ [50, 51].

As suggested by Cremer et al. in a small series of patients, daily pharmacological manipulations of CPP are suggested to determine the dynamic changes in CPP requirements [52]. Unfortunately, this small series of patients was heterogeneous in terms of underlying injuries and concomitant therapeutic interventions.

Present conclusions. Despite the beneficial effects reported upon rigid dichotomy of CPP- versus ICP-targeted therapy, the dynamic pathologic processes with their strong temporal and lesion dependency might require a more flexible approach allowing a combination of the CPP- versus ICP-targeted treatment strategies.

Hyperventilation

Initially envisioned as an elegant way to control ICP by simply increasing ventilation frequency or tidal volumes in mechanically ventilated patients, the therapeutic hyperventilation has been subject to controversial discussions, as hypocapnia can induce adverse effects and contribute to a worse outcome. In this context, vasoconstriction with ensuing or impending ischemia as evidenced by decreases in cerebral perfusion [21, 53], reduced $ptiO_2$ and $SjvO_2$ values [25], and increased extracellular glutamate and lactate concentrations [53] have been reported. As shown by Carmona Suazo et al., daily short hyperventilation trials of 15 min reveal an increasing risk for hyperventilation-induced compromise of cerebral oxygenation during the first 5 days as reflected by an elevated $ptiO_2/paCO_2$ reactivity ratio [54]. As suggested by Coles et al., threshold value of $paCO_2$ ranges from 34 to 38 mmHg (= 4.5–5.0 kPa), implying that even small changes in $paCO_2$ during normoventilation with normocapnic values can induce unfavorable alterations [21]. Other groups, however, did not report any adverse effects and highlight a consistent decrease in ICP [55]. Brief episodes of hyperventilation which reduced posttraumatic cerebral perfusion were not associated with energy failure, even in regions where ischemic perfusion values were reached. Thus, Diringer

et al. concluded that underlying suppressed metabolism protects from hyperventilation-induced impaired perfusion [56].

Due to extensive experience gained within the past 20 years, the official AANS guidelines suggest that chronic hyperventilation should definitely not be performed during the first 5 days following TBI. In particular, hyperventilation should definitely be avoided within the first 24 h, as this time period is characterized by impaired cerebral perfusion and disturbed metabolic and energetic homeostasis. Hyperventilation decreases the already impaired perfusion even further, limiting nutritional supply and oxygenation to damaged tissue, and may also induce lesion growth by disturbing cerebral vasoreactivity and autoregulation. This may be of utmost importance in patients with more severe injuries as e.g., SDH and multiple contusions in whom vascular responsiveness to CO_2 is reduced [57, 58]. In addition, hypocapnia can also impair cardiac, pulmonary and cardiovascular function [59].

Present conclusions. As concluded by a Cochrane review, randomized controlled trials are required to assess the effectiveness of hyperventilation [60]. Hyperventilation might only be an option if detailed assessment of individual perfusion and metabolism pattern is available. Specific bedside monitoring is definitely indispensable, since even small changes in $paCO_2$ within its normal range can already induce adverse effects.

Osmotherapy: Mannitol and Small-Volume Resuscitation

Shifting of electrolytes and changes in osmotic gradients across the blood-brain barrier contribute to brain edema and brain swelling. Thus, manipulation of this osmotic gradient appears to be a feasible therapeutic approach. In this context, mannitol and hypertonic saline solution with and without dextran have been investigated under clinical conditions. Despite extensive experience with mannitol it still lacks evidence of efficacy, as concluded by a recent Cochrane review [61]. Mannitol with its strong osmotic potential expands plasma, thereby reducing the hematocrit and blood viscosity, and increases CBF and oxygen delivery within several minutes following its administration. These effects are predominant in patients with CPP values < 70 mmHg and reduced serum osmolarity [62]. Ultra-early administration of high-dose mannitol (1.4 g/kg) in the emergency room appears superior to low-dose mannitol (0.7 g/kg) to reverse clinical signs of impending brain death and improve long-term neurologic outcome, as studied in severely injured patients with a Glasgow Coma Scale score of 3 and bilateral abnormal pupillary widening [63]. Continuous infusion should be avoided, as mannitol may damage the blood-brain barrier or accumulate within the extracellular space which, in turn, could raise brain osmolality, thereby exacerbating ICP and increasing brain swelling.

An alternative to mannitol are hypertonic solutions, referred to as small-volume resuscitation, as a small dose, usually 4 ml/kg body weight (approximately 250 ml) of 7.2–7.5% NaCl/colloid solution is infused in approximately 20 min. In addition to its primary resuscitative potential from trauma and hypotensive shock, this approach might also gain access to perioperative and intensive care treatment of patients with elevated ICP as suggested by Kreimeier & Messmer [64]. The high tonicity and the fact that hypertonic saline does not penetrate the blood-brain barrier makes it a promising osmotherapeutic agent. The decrease in ICP is thought to result from reduced water content in noninjured brain areas and the cerebellum without significantly changing global cerebral perfusion [65]. The transient reduction in ICP might be prolonged by continuous infusion but requires careful control to avoid adverse effects as e.g., electrolyte abnormalities, cardiac failure, bleeding diathesis, phlebitis, central pontine myelinolysis, and rebound intracranial hypertension following uncontrolled infusion.

As recently published, administration of hypertonic saline solution results in superior effects compared to mannitol by decreasing daily episodes of intracranial hypertension with a reduced rate in therapy-refractory increases in ICP [66]. However, morbidity and mortality were similar in both groups and the difference in osmotic strength (350 mOsmol/dose vs. 175 mOsmol/dose) limits the power of this study. As suggested by Horn et al., hypertonic saline solution might be an effective measure to decrease ICP which is otherwise refractory to standard therapeutic approaches, i.e., mannitol and barbiturates [67]. When administered during the prehospital phase, hypertonic saline solution did not result in improved mortality or morbidity, as seen in a double-blind, randomized controlled trial enrolling 229 comatose and hypotensive TBI patients [68].

In a recently published pilot study, equimolar doses of hypertonic saline and dextran solution (HSD, Res-

cueflow) were compared to 20% mannitol solution. HSD caused a significantly greater decrease in ICP than mannitol and had a longer duration of effect than mannitol [69].

Present conclusions. As concluded in two recently published Cochrane database reviews, further detailed prospective, randomized, and blinded large-scale clinical studies are required to determine if the wide confidence intervals observed in the present investigations will reveal if hypertonic solutions are of significant importance [70] and if mannitol is indicated to manage intracranial hypertension in patients without an operable intracranial hematoma [61]. In this context, this treatment modality needs to be investigated before admission, at various time points following admission to the hospital in dependence of underlying lesion, and in regard to intracranial hypertension.

Choice of Volume to Increase CPP

To date, it is well accepted that volume infusion to correct hemodynamic stability should precede administration of vasopressors. However, the type and amount of fluids are still under debate. As recently shown, normovolemia with a fluid balance ranging from –594 to 4,859 ml was associated with the least incidence of poor outcome in hypothermic as well as normothermic patients compared to patients with lower or higher fluid balance [47]. Unfortunately, data of volume balance in patients treated according to the "Lund concept" are not available which might allow to more efficiently define required normovolemia in patients with severe TBI. Due to its plasma-expanding effects, colloid solutions are superior to crystalloid solutions which need to be administered in higher amounts to induce similar hemodynamic stability. As recently published, high amounts of hydroxyethyl starch administered repeatedly in severe TBI patients are safe [71]. As reported by the Saline versus Albumin Evaluation study, 4% albumin was not associated with an overall benefit compared to saline. However, patients with severe TBI within the albumin-treated group revealed a trend toward increased mortality [72].

Present conclusions. The ideal fluid balance remains to be determined in patients suffering from severe TBI. Providing a lower CPP can be adequately controlled and justified by specific monitoring, a timely reduction in volume administration might attenuate side effects, as e.g., ARDS known to increase morbidity in these patients.

Barbiturate Coma

Barbiturates can decrease elevated ICP in patients presenting with otherwise therapy-refractory intracranial hypertension by reducing cerebral metabolism and oxygen consumption, thereby decreasing vascular tone, inhibiting excitatory input and energetic impairment. However, adverse systemic side effects which can lead to serious complications related to hemodynamic instability and infections due to impaired immunocompetence limit the administration to most extreme situations. The fact that patients can suffer from further episodes of increased ICP despite complete suppression of neuronal activity as evidenced by continuous EEG recording and an initial responsiveness, suggests that barbiturate coma might not be the ultimate step in our therapeutic hierarchy but might require additional specific treatment approaches. In this context, we must comprehend that EEG monitoring employed to guide barbiturate administration will only reflect changes in cortical neuronal activity. Alterations occurring in deep structures or involving astrocytes which encompass nearly 75% of the brain remain disguised. As observed under experimental conditions, barbiturates dose-dependently decrease astrocytic clearance of glutamate [73], possibly resulting in additional functional and structural cell damage, as glutamate cannot be used to fuel intracellular energetic processes or aid in synthesizing the antioxidant glutathione. Under clinical conditions, this, in turn, could result in increased energetic impairment as reflected by sustained cerebral oxygen extraction, progressing edema formation, and further increase in ICP. This increase in ICP during barbiturate coma could also stem from hyperemia, if CPP is not adjusted to the lowered metabolic demand during barbiturate coma. The statement published within the official AANS guidelines that prophylactic administration of barbiturates is not indicated following severe TBI is questioned by the "Lund concept" and the fact that many features within the overall intensive care treatment of these patients have changed due to extensive pathophysiological characterization of the different features of TBI and development of specific treatment options. Controlling energetic impairment and deterioration by suppressing cerebral metabolism through co-infusion of low-dose thiopental could prevent progression of structural and functional cell damage and

reduce the risk of CPP-dependent increases in cerebral blood volume, as a lower CPP can be tolerated [74]. This hypothesis needs to be prospectively investigated at different centers.

Present conclusions. As concluded in a Cochrane database review published in 2000, barbiturate coma does not improve outcome in patients with severe TBI owing to its hypotensive effect [75]. Prophylactic barbiturate administration discouraged by the AANS, however, is challenged by the "Lund concept" and awaits detailed investigation. More detailed investigations using refined monitoring techniques and modern knowledge are required to determine the benefit of initial low-dose barbiturate administration, at which ICP high-dose barbiturate coma is to be initiated, for how long barbiturate coma (low and high dose) needs to be maintained, and what level of neuronal suppression as determined by continuous EEG recording and metabolic/neurochemical supervision is adequate.

Sedation and Analgesia

Following severe TBI, the injured brain is highly vulnerable to any potentially adverse influence. In this context, coughing and straining exert a certain mechanical stress due to an increase in ICP caused by decreased venous outflow [76]. This, in turn, carries the risk of causing additional hemorrhages and aggravating existing space-occupying lesions, thereby adding to the underlying pathologic vicious circle of compression and edema formation. In addition, a concomitant increase in oxygen consumption reflected by decreased $SjvO_2$ in face of reduced CPP may occur during coughing while endotracheal suctioning inadequately sedated TBI patients [76].

Sustained cellular activity is an energetically compromising condition of stress which adds to a depletion of energetic reserves, thereby reducing the threshold for additional, otherwise tolerable compromising events. To date, neurons with their different excitatory and inhibitory circuit receptors remain the primary direct pharmacological target although astrocytes account for a large portion of energy-consuming and -producing effects, owing to their plethora of different functions within the neuronal-glial-endothelial syncytium [77].

A common manner to counteract these stress-related changes and thus prevent additional injury is to induce and maintain adequate analgesia and sedation. As outlined by Citerio & Cormio [78], many pharmacological agents with characteristic differences in their pharmacokinetic and pharmacodynamic profile are available to specifically control ICP and cerebral metabolism and reduce seizure activity in addition to the more general aims of controlling pain, anxiety, and agitation, limiting the stress response, facilitating care, and managing ventilatory support. For brain-injured patients it is important to maintain adequate supply with nutrients and oxygen to guarantee sufficient energy production. Besides increasing oxygen delivery by optimized hemodynamics, ventilation, and oxygen carriers, oxygen consumption and demand are reduced by decreasing cerebral metabolism. Providing an intact metabolism-flow coupling, a reduction in cerebral metabolism will decrease CBF, thereby reducing cerebral blood volume and ICP. In this context, it is important to remember that metabolism is suppressed dose-dependently until the EEG becomes isoelectric. Thereafter, minimal basal energy consumption cannot be suppressed any further. Thus, reduction of intracranial blood volume is also restricted.

In general, benzodiazepines (e.g., midazolam, lorazepam) or propofol are combined with opioids (e.g., morphine, fentanyl). As recently shown, disturbances in metabolism and metabolic suppression reactivity quantified by transient propofol-induced burst suppression pattern are heterogeneous and influenced by underlying brain lesions [79].

On a cellular level opioids activate specific μ-, δ-, κ-, and σ-receptors, of which μ-receptors mediate analgesia by inhibiting presynaptic release of excitatory transmitters via decreased availability of calcium and stabilizing postsynaptic membranes by increasing permeability for potassium. While activation of μ-receptors reduces liberation of norepinephrine and substance P, δ-receptors attenuate release of acetylcholine, and κ-receptors decrease liberation of dopamine.

Benzodiazepines require the endogenous inhibitory transmitter GABA (γ-aminobutyric acid) to increase the opening time of the chloride channel by allosteric modulation of the $GABA_A$ receptor. This results in a stabilization of pre- and postsynaptic membranes, by which excitatory inputs are blunted.

Propofol has several targets, as it directly activates $GABA_A$ receptors, inhibits the NMDA (N-methyl-D-aspartate) receptor and modulates calcium influx through slow calcium ion channels [80].

Overall, the choice of agent, dosage, and duration of administration show a strong variability between coun-

tries and hospitals which might have contributed to the failure of various pharmacological trials aimed at modulating/inhibiting transmitter-mediated influences [81]. Some favor propofol to treat intracranial hypertension, as it dose-dependently reduces EEG activity. Others prefer benzodiazepines despite their "ceiling effect" in reducing cerebral metabolism and blood flow in fear of propofol-induced increase in hemodynamic instability, lipid load, and the potentially fatal "propofol infusion syndrome" characterized by severe metabolic acidosis, cardiac and peripheral muscle damage (necrosis), and circulatory collapse. This syndrome can be provoked by elevated catecholamine, glucocorticoid and cytokine levels [82] encountered in patients with severe TBI and is thought to be related to disturbed structural and functional integrity of mitochondria [80].

The beneficial effects of these drugs in terms of reducing cerebral metabolism and oxygen consumption are confronted with certain side effects. The most common problem is receptor desensitization or downregulation developing during chronic continuous administration of opioids and benzodiazepines which accounts for the diminishing effectiveness of these drugs as evidenced by coughing, straining and eye opening despite continuously infusing these drugs at their maximally recommended dose. In clinical practice, dosage of opioids and benzodiazepines is increased following changes in ICP (Figure 5), suggesting that starting with higher or submaximal dose or adding a more potent sedating agent as e.g., low-dose thiopental as advocated by the "Lund concept" [42] might prevent further cellular deterioration known to contribute to subsequent intracranial hypertension. Contrary to benzodiazepines, barbiturates activate $GABA_A$ receptors independently of GABA (at high dosage). Since CSF glutamate and hypoxanthine concentrations remained unchanged and even showed a trend to elevated levels during continuous administration of midazolam and fentanyl (Figure 5) and since thiopental significantly reduced CSF glutamate and hypoxanthine in patients who developed therapy-refractory intracranial hypertension during administration of fentanyl and midazolam [15], a combination of these drugs might be a more promising approach in conveying neuroprotection.

A further complication is drug-induced reduction in bowel function leading to impaired transport and uptake of nutrients which compromises nutritional supply of energetic compounds. In addition, disturbed bowel function may even progress to paralytic ileus. Serious constipation might add to intracranial hypertension by elevating intraabdominal pressure known to reduce cerebral venous outflow. Furthermore, prolonged administration of opioids may suppress pituitary function, thereby disturbing the hypothalamic-pituitary-adrenal axis, causing hormonal dysregulation, and suppression of the immune system [83].

While inducing and maintaining sedation in patients with severe TBI is a rather straightforward approach, the awakening phase might be underestimated in its pathophysiological importance. In this context, continuous administration of opioids and benzodiazepines induces tolerance and dependency due to altered receptor function and expression. Clinically, patients are extremely stressed upon reduction or discontinuation of drugs. The observed psychovegetative dysregulation resulting in hyperdynamic circulation, fever, and physical agitation might again endanger cerebral viability. Usually, neuromonitoring has already been discontinued, leaving us without any data for this serious phase. In general, administration of the α_2-adrenergic agonist clonidine is used to attenuate these alterations.

Present conclusions. To date, choice, dosage, and length of administered analgetics and sedatives are at the discretion of individual centers. A standardized protocol might improve comparability of patients in multicenter studies. Since level of sedation assessed by EEG activity is judged as incomplete upon administration of benzodiazepines, specific receptor modulation might regain importance when aiming at metabolic stability to reduce intracranial hypertension and increase survival rate rather than anticipating complete restoration of higher cognitive functions. More detailed investigations are required to determine potential adverse effects during the arousal phase overshadowed by withdrawal symptoms which might destroy previous successful protection.

Fever, Therapeutic Hypothermia, and Temperature Control

Based on experimental and clinical data, increases in rectal temperature > 38.5 °C corresponding to brain temperature levels of 40–41 °C are associated with adverse biochemical alterations leading to functional and structural deterioration, resulting in increased posttraumatic morbidity and mortality [84]. Consequently, controlled normothermia of body and brain as well as prevention of fever are considered important basic

treatment modalities in modern therapy of patients with severe TBI [84]. The next logical step was to induce hypothermia by which reduced cerebral metabolism might convey protective effects. However, therapeutic hypothermia following severe TBI could not reproduce the beneficial effects observed in patients with cardiac arrest who had been cooled to 32–33 °C for 24 h [85]. In a recently published carefully conducted clinical study, Tokutomi et al. [86] concluded that maintaining rectal temperature between 35 and 35.5 °C results in an optimal relationship between decreased ICP, metabolic suppression, adequate cerebral perfusion, and least systemic side effects known to offset anticipated protection once body temperature drops to < 35 °C [87].

As observed with the administration of sedatives and analgetics, induction and maintenance of hypothermia and rewarming are at the discretion of different centers and reveal strong variations [88]. In this context, beginning, degree and length of hypothermia, means to induce hypothermia, and speed of rewarming need to be redefined. Some favor normothermia (37–38 °C) which, however, is associated with elevated ICP [86], while others maintain body temperature between 35 and 37 °C. Other groups will only initiate deep hypothermia (32–34 °C) in patients requiring barbiturate coma due to refractory intracranial hypertension [89]. Rewarming ranges from 1 °C/d to 1 °C/h [88]. Furthermore, the technique of measuring temperature shows a strong variability between centers. In this context, brain temperature is accepted to exceed body core temperature determined in the jugular bulb, pulmonary artery, esophagus, tympanic membrane, and bladder by 2 °C, which means that we might be underestimating intracerebral changes.

Fever or temperature control also differs strongly between institutions. While some centers propagate early administration of the antipyretic drugs acetaminophen and ibuprofen directly upon admission, other centers are more reluctant to give these antipyretic drugs to avoid possible adverse side effects in ICU patients.

The least expensive way to reduce body temperature is to use surface cooling blankets. However, this method results in episodes of difficult-to-control decreases and increases in body temperature, sometimes > 2 °C within a few hours. In addition, body temperature usually increases abruptly within a few hours to levels > 38 °C. In the meantime, more sophisticated techniques have been developed, ranging from hydrogel-coated water-circulating energy transfer pads applied directly to the trunk and thighs [90] to special cooling helmets [91] and endovascular cooling employing heat exchange catheters [92] which are superior in terms of controlling temperature during hypothermia and rewarming.

Present conclusions. The need to prevent fever is unanimously accepted. However, therapeutic hypothermia remains a topic fueling controversial discussions. To date, degree of hypothermia, means and time point of inducing as well as maintaining hypothermia are at the discretion of individual centers, requiring a standardized protocol, also referring to use of antipyretic drugs. It remains to be determined if quantitative or qualitative changes in body temperature during maintained hypothermia are harmful, which speed of rewarming is allowed without inducing additional injuries, and if neuromonitoring needs to be extended to the post-rewarming phase.

Elevated Intraabdominal Pressure

In recent years, clinical awareness concerning deleterious effects of intraabdominal hypertension on nearly all organ systems has prompted different means of treatment, ranging from curarization to application of external negative abdominal pressure and surgical decompression [93] which have been shown to reduce ICP and decrease mortality [94]. Following TBI, abdominal hypertension has been shown to elevate ICP and decrease CPP closely following the dynamics and kinetics of the intraabdominal pressure which is of high concern in patients presenting with already increased ICP [95].

Dysregulated bowel movements may also contribute to abdominal hypertension. In this context, our own investigations suggest that some patients might also profit from enemas, as elevated ICP was significantly decreased from 22 ± 9 to 13 ± 7 mmHg for a median duration of 4 h (1–23 h) in 38% of prospectively investigated 67 patients with severe TBI. These results reveal that exploited intracranial compensatory mechanisms to counteract elevated ICP strongly depend on measures which can decrease pressure load transmitted from lower body cavities by improving cerebral venous outflow.

As recently shown, the composition of the enema used might also directly influence the cerebral compartment as cerebral extracellular glycerol was significantly increased [96]. Whether the absorbed glycerol is able to equally reduce elevated ICP and improve CPP as observed following intravenous infusion remains to be determined.

Present conclusions. Mechanistically, intraabdominal hypertension following fluid overload or dysregulated bowel movements contributes to intracranial hypertension. Prospective, randomized studies are needed to determine if prophylactic measures are required and which interventions need to follow a standardized protocol.

Steroids

Ever since its identification to inhibit the activity of phospholipase A_2, thus preventing downstream generation of various destructive prostaglandins and leukotrienes, steroids were praised for their antiedematous potency. This beneficial action as documented for brain tumors, however, has been subject to controversial discussions for TBI patients. As shown by the recently published results of the international multicenter, prospective, randomized, and double-blind study CRASH, this issue has finally been resolved. In this study, 10,008 patients with mild and severe TBI were randomized to receive methylprednisolone (loading dose 2 g/first hour, followed by 0.4 g/h for the following 48 h) or placebo. With 5,007 patients in the verum and 5,001 in the placebo group, mortality was significantly increased during the initial 2 weeks following injury with a trend to a higher incidence in seizure activity, gastrointestinal hemorrhages, wound infections, and pneumonia in patients receiving the steroid [97]. Given the plethora of different side effects which are possibly potentiated by other drugs, as e.g., catecholamines and certain pathologic alterations which are characteristic of severely injured critical care patients, as e.g., peripheral insulin resistance, increased energy expenditure with hormonal, inflammatory, and immunologic dysfunction, steroids should no longer be considered for acute cerebral (and spinal) injuries. In this context, glucocorticoids inhibit the cellular and humoral immune response, decrease insulin responsiveness of muscle and fat tissue, increase blood glucose levels, decrease muscle mass, may promote myo- and neuropathy, disturb plasma electrolytes via their mineralocorticoid effects, and can hamper the function of the hypothalamic-pituitary-adrenal axis which can already be disturbed by TBI itself. Under experimental conditions, glucocorticoids have been shown to aggravate underlying brain damage by increasing metabolic vulnerability in neurons due to inhibition of glucose uptake, exacerbating glutamate-induced excitotoxicity, disrupting mobilization of neurotrophins, inhibiting the local inflammatory response [98], and reducing cerebral antioxidative capacity [99].

Present conclusions. Contrary to the hypothesized improved outcome following TBI, the large multicenter, placebo-controlled, double-blind study conducted by the MRC CRASH trial has negated its implementation within the standard treatment regimen of patients with severe TBI.

Hormonal Dysregulation

TBI is associated with structural and functional disturbances of the hypothalamic-pituitary-adrenal axis resulting in diminished blood levels of various hormones originating from the anterior and posterior pituitary. These disturbances which depend on the severity of underlying TBI [100] occur early after TBI [101] and have been shown to persist up to 5 years [100, 102, 103]. Due to prolonged persistence of these endocrinological alterations and the fact that these disorders contributing to morbidity following TBI are treatable, more detailed investigations to determine need and efficacy of corrective treatment paradigms starting during the intensive care phase must be conducted [100, 102].

Structural disturbances can result from hemorrhages and infarctions of the pituitary or hypothalamus as well as traumatic stalk resections. Functional disturbances can result from sustained or impaired feedback inhibition or continuous activation by routinely administered drugs (e.g., opioids, catecholamines). In this context, exogenously administered dopamine can induce hypopituitarism reflected by suppression of circulating concentrations of all anterior pituitary-dependent hormones [104] and noradrenaline might contribute to the observed adrenal insufficiency [105]. Disturbances of the anterior and posterior pituitary can result in significant changes in blood electrolyte levels which, in turn, can induce edema formation and aggravate preexisting edema due concomitant osmotic shifts (hypo- and hypernatremia), upregulation of glial aquaporin (hyponatremia), and changes in volume-regulatory osmolytes (taurine, glutamate, aspartate, glutamine) leading to sustained intracellular water accumulation. Blunted or sustained release of the antidiuretic hormone (ADH) from the posterior pituitary gland results in increased and decreased plasma sodium levels, respectively. Apart from TBI-induced alterations, barbiturates and opioids are also known to stimulate release of ADH. Sustained TBI-induced stimulation of the anterior pituitary gland

results in elevated liberation of adrenocorticotropic hormone (ACTH) which increases release of cortisol and aldosterone from the adrenal gland. Hyperaldosteronemia results in hyponatremia. Diminished production of aldosterone due to blunted stimulation of the adrenal gland caused e.g., by hypothalamic or pituitary damage with subsequent diminished release of ACTH or irresponsiveness of the adrenal gland to ACTH due to receptor downregulation following prolonged stimulation can result in hyponatremia, hyperkalemia, hypermagnesemia, and acidosis. This, in turn, can result in hypotonic dehydration and disturbed vascular autoregulation via developing acidosis. Hypoaldosteronemia can also result from opioid administration or sustained negative feedback via elevated circulating cortisol levels.

On a cellular level, various mechanisms have been identified to contribute to edema development following dysnatremia. In this context, osmoregulatory osmolytes and water transport channels are highlighted. Under conditions of hypertonic stress as seen with hypernatremia, the first cellular response is to shrink as water leaves the cell until a new balance between intra- and extracellular osmolality has been reached. Thereafter, uptake of electrolytes with increased intracellular osmolality and water uptake restores original cell volume. This fast response is mainly observed during transient (acute) hypertonic stress and is associated with an activation of various energy-consuming electrolyte transporter proteins [106]. However, this pathologically increased intracellular ionic burden can impair functional and structural integrity of these cells. Under conditions of prolonged hypertonic stress which is clinically relevant when hypernatremia persists > 24 h, secondary adaptation process, i.e., energy-dependent accumulation of organic osmolytes is then initiated in exchange for electrolytes. The energy dependency of these adaptive mechanisms in face of underlying compromised metabolism and disturbed cellular functionality might not result in normalized cell volume but persisting cellular edema. If hypernatremia is corrected too rapidly (> 0.5 mmol/l/h), water will be driven into the cerebral extracellular space, resulting in sustained cellular edema formation, as neurons and astrocytes had previously accumulated organic osmolytes. Restoration of normal intracellular composition is accepted to last for at least 5–7 days. In case of hypotonic stress, i.e., hyponatremia, the initial response in cellular swelling is followed by a subsequent release of various organic osmolytes as an unspecific response of cells to reinstate a balanced intra- and extracellular osmolality [107]. The magnitude of this response depends on the speed at which hyponatremia develops. The release of osmolytes, especially glutamate and aspartate known for their excitotoxic potential, might damage the already injured brain tissue following TBI even further. If this hyponatremia is corrected too fast, a relative and absolute hypernatremia can then induce pathologic alterations as outlined above.

From our own experience, patients can go through phases dominated by isolated hypo- and hypernatremia or sequential changes with preceding or following hypo- and hypernatremia, respectively. These phases appear to be self-limited, as no specific, i.e., hormonal correction was performed. In a series of 40 consecutively investigated patients with severe TBI, 13% developed hyponatremia and 28% presented with hypernatremia. ICP was lowest in patients with plasma sodium concentrations ranging from 120 to 129 mmol/l (16 ± 1 mmHg) and remained at 18 ± 1 mmHg when plasma sodium levels ranged from 130 to 155 mmol/l. However, plasma sodium levels > 155 mmol/l were associated with significantly increased ICP values (24 ± 1 mmHg). Plasma sodium > 165 mmol/l was associated with death due to therapy-refractory intracranial hypertension.

As pointed out in various reviews, it is essential to slowly correct the dysnatremias to avoid worsening or induction of neurologic damage. Apart from symptomatic therapies by slowly infusing NaCl or restricting volume administration – which might be difficult in hemodynamically unstable patients or those requiring volume to maintain adequate CPP – pharmacological interventions using oral vasopressin receptor antagonists [108] or low-dose aldosterone antagonists to correct hyponatremia and hypernatremia, respectively, might be valuable alternatives.

Since any cell is capable of regulating its volume through shifting of water, electrolytes and volume-regulatory osmolytes (e.g., glutamate, taurine) [109], we might be able to use isolated erythrocytes to determine the effects of hyper- and hyponatremia, and to also guide the speed of correction allowing to adapt specific or symptomatic therapeutic interventions accordingly. Since these critically ill patients might also depict other hormonal disturbances [105] suppressing the adrenal responsiveness to corticotropin-releasing hormone (CRH) and release of cortisol, replacement therapy with low-dose hydrocortisone with its mineralocorticoid effects might be considered an option in these patients presenting with hyponatremia.

Present conclusions. Following severe TBI, hormonal disturbances can induce dysnatremias which, in turn, can contribute to intracranial hypertension. Routinely, specific diagnostic tests are only performed when dysnatremias are present. Maybe daily analysis might aid in detecting ensuing changes. To date, only symptomatic approaches are available to slowly correct dysnatremias. This, however, is associated with the risk of strong variations. It remains to be determined if pharmacological interventions might result in a superior controlled correction. Given the volume-regulatory response encountered in any cell, erythrocytes might be used to control correction of dysnatremias by measuring the release of volume-regulatory osmolytes as e.g., glutamate and taurine in addition to assessing changes in cell volume.

Nutrition: Possible Consequences on Intracranial Pathology

Hormonal dysregulation observed in any critically ill patient is more sustained in patients with severe TBI as judged by the increased energy expenditure [110]. To counteract the ensuing catabolism, various enteral and parenteral nutrition solutions have been developed to ameliorate weight loss, negative nitrogen balance, immune dysfunction, increased infection rate, thereby improving morbidity and mortality. However, some of the amino acid components, i.e., glutamate and arginine, might exert a negative impact on the already compromised intracranial compartment. In this context, glutamate might penetrate the cerebral extracellular space and possibly contribute to cytotoxic edema formation owing to its excitotoxic potential. Arginine, the physiological precursor of the vasodilating nitric oxide (NO), could induce intracranial hypertension. Infusing a commercially available glutamate-containing amino acid solution doubled plasma glutamate levels within 2 h compared to a glutamate-free solution [111]. Intravenous infusion of a glutamate- and arginine-enriched amino acid solution significantly elevated corresponding plasma levels [112]. Interestingly, repetitive infusions were associated with a progressive increase in plasma levels over time. To date, it is unclear if the potential pathophysiological importance of these alterations might detract from the beneficial effects in terms of significant decrease in skeletal muscle myofibrillar catabolism and positive nitrogen balance.

Glutamine is a semi-essential amino acid which becomes indispensable under pathologic conditions. Its supplementation has been reported to enhance cellular immunologic functions, increase survival, and attenuate muscle catabolism and intestinal dysfunction [113]. Subsequent metabolism of enterally or parenterally administered glutamine to glutamate and arginine is feared, as these amino acids could induce or aggravate underlying injury mediated by excitotoxicity and vasodilation, respectively. In this context, enteral glutamine infusion via a double-lumen nasojejunal tube significantly and dose-dependently increased plasma glutamate concentrations [114]. To date, the glutamine-driven increase in jugular venous glutamate as reported by Petersen et al. in 1996 [115] has neither been confirmed nor disputed. To date, it remains unclear whether enteral or parenteral supplementation with low-dose glutamine with its immunosupportive potential increases arterial plasma glutamate levels, thereby potentially endangering the already injured brain.

A mismatch between aromatic amino acids (methionine, phenylalanine, tryptophane, tyrosine) and branched-chain amino acids (leucine, isoleucine, valine) within the group of neutral amino acids contributes to metabolic encephalopathy, as these amino acids compete for the same transporter located at the blood-brain barrier. A relative increase in aromatic amino acids displaces the branched-chain amino acids, thereby impairing detoxification of produced NH_4^+ and promoting sustained production of excitatory transmitters (dopamine, norepinephrine, serotonin) and synthesis of false neurotransmitters (tyramine, phenylethanolamine, tryptamine). A relative increase in branched-chain amino acids, in turn, decreases the availability of catecholamine precursors which could produce biochemical and neuropsychological changes consistent with impaired dopamine neurotransmission [116]. Taken together, these alterations could aggravate underlying damage which might require more specific pharmacological intervention or adaptation of the nutrition.

Present conclusions. Nutritional support is essential in attenuating evolving catabolism. Whether ingredients of enteral and parenteral solutions might compromise intracerebal pathology even further by e.g., elevating plasma glutamate and arginine concentrations or increasing a mismatch between aromatic and branched-chain amino acids requires further detailed investigations. The time point at which administration of glutamine following severe TBI may be adequate to

support immunologic competence remains to be determined.

Hyperglycemia

Overall, both low and high blood glucose levels can aggravate underlying brain damage, increase edema formation, thereby contributing to intracranial hypertension.

A large body of evidence underscores the adverse effects of increased blood glucose levels following severe TBI, implementing that prevention of hyperglycemia will aid in preventing brain tissue acidosis [117] and avoiding worsened ouctome [118]. On a cellular level within the central nervous system, sustained hyperglycemia results in an accelerated uptake and subsequent metabolism of glia and neurons known to be overly active following TBI, especially within pericontusional areas [119]. This, in turn, might increase lactate production, if oxidative degradation of glucose is hampered due to impaired mitochondrial function and compromised citric acid cycle, thus fueling ATP (adenosine triphosphate) production via the alternative pathway when pyruvate is transformed to lactate via lactate dehydrogenase (LHD). Production of lactate decreases brain tissue pH which may deactivate various enzymes, activate destructive intracellular cascades and energy-consuming pumps, thereby impairing functional and structural integrity of the brain in face of its limited energetic reserves even further. As suggested by the recently published results by the group of Christian Nordström only hyperglycemic values > 15 mmol/l are associated with a moderate increase in interstitial lactate levels [120].

In the critically ill, accelerated glucose toxicity is attributed to a cellular glucose overload in organs and cells known for their insulin-independent glucose uptake involving not only the central and peripheral nervous system, but also hepatocytes, endothelial, epithelial, and immune cells. Sustained oxidative phosphorylation can result in peroxynitrite generation which, in turn, damages mitochondria and impairs various intracellular enzymes [121]. Furthermore, hyperglycemia can induce functional incapacitation of the cellular and humoral inflammatory/immune response. The concept of maintaining blood glucose at low levels within tight limits (80–110 mg/dl = 4.4–6.1 mmol/l) reported to reduce mortality and morbidity in any patient with chronic and acute nondiabetic disease requiring intensive care treatment [122] has also been propagated to be beneficial following severe TBI. However, the actual data for this subpopulation has not been described in detail to date.

Glucose uptake strongly depends on the involved glucose transporters with their differentiated functionality and regulatory features, and their characteristic distribution between and within different organs. Within the central nervous system virtually all glucose transporters (GLUT) are expressed [123]. GLUT1 is mainly found on astrocytes and endothelial cells, GLUT2 is localized on astrocytes, and GLUT3 is predominantly expressed by neurons. The amount of expressed high-affinity GLUT1 and GLUT3 strongly influences the rate of glucose uptake. An upregulated expression of these glucose transporters could mediate glucose toxicity at normal or even low glucose levels. By contrast, the rate of glucose uptake by the low-affinity GLUT2 increases in parallel with the rise in blood glucose, thus markedly endangering GLUT2-carrying cells, i.e., astrocytes, through glucose-mediated cell damage. Conversely, a decrease in blood glucose could result in reduced cerebral uptake. Glucose uptake can be controlled by down- or upregulation of expressed transporter proteins [124]. In this context, hyperglycemia downregulates GLUT1 while chronic hypoglycemia upregulates GLUT1. In addition, hypoxia upregulates GLUT1 and GLUT3 to provide the cell with sufficient amounts of glucose in face of damaged mitochondria. As recently shown, glucose transport determined by ^{18}F-FDG (fluorine-18-labeled fluorodeoxyglucose) kinetic modeling was significantly reduced within pericontusional cortex [119]. In addition to the described regional heterogeneity an interindividual variability with an increased pericontusional ^{18}F-FDG uptake was observed in five of the 21 studied patients.

Induction and maintenance of low blood glucose levels require administration of high doses of insulin especially during the early posttraumatic phase which is dominated by skeletal and hepatic insulin resistance and hormonal dysregulation. While van den Berghe et al. do not report hypoglycemic episodes [121], this possibility remains of utmost importance, since a decrease in blood glucose levels to < 4.9 mmol/l [125, 126] increases postischemic seizures and peri-infarct depolarizations known to further impair tissue viability and also increase mortality under experimental conditions. As just recently published, the regional and temporal heterogeneous disturbance in cerebral metabolism associated with low extracellular glucose concentrations was

associated with an increased rate of spreading-depression-like events in the perilesional cortex which might contribute to an increased mortality in TBI patients [127].

Retrospective analysis of 30 patients with severe TBI revealed that approximately 34% of 1,630 blood glucose values documented in 4-hourly intervals exceeded the upper limit of 6.1 mmol/l, reflecting that even continuous insulin administration fails to completely control blood glucose levels. Attributed to the administered insulin, we observed hypoglycemic values in approximately 8%. If we consider 5 mmol/l a more appropriate lower limit to prevent uncontrolled depolarizations [126], we would have then induced endangering situations in approximately 22% of the 1,630 values.

Present conclusions. Fueled by recent clinical trials and experimental studies, the optimal limits for blood glucose levels need to be defined to assure least adverse effects for the already impaired energetic cerebral homeostasis. Detailed clinical and experimental studies are required to determine which variations in blood glucose are tolerable, at which speed these changes are allowed to occur without inducing adverse side effects, and if there is a temporal dependency influenced not only by resolution of the catabolic postaggression phase but also by strong daily and circadian variations in energetic supply.

Potential New Approaches

Improving oxygen delivery remains an area of interest which goes through phases of controversial popularity. In this context, experimental data suggest that resuscitation with diaspirin cross-linked hemoglobin, a hemoglobin-based oxygen carrier with pressor activity, might dose-dependently decrease ICP and increase CPP as observed in a combined model of TBI and hemorrhagic shock. However, the reduced cardiac performance might become limiting under clinical conditions [128].

Hyperbaric as well as normobaric hyperoxia have been reported to attenuate signs of impaired metabolism and also improve outcome in patients with severe TBI [129, 130]. However, these approaches are overshadowed by certain limitations and by findings ruling out a beneficial effect based on microdialysis studies [131]. Hyperbaric oxygenation requires special chambers with addditional technical, logistic, and academic support. Although normobaric hyperoxia is easy to perform, both interventions might induce vast tissue damage via generated oxygen radicals, induced stress response, activated pro-inflammatory cytokines, and initiated intracellular destructive cascades [132].

The majority of patients suffering from severe TBI present with systemic and/or intracranial hemorrhages which can progress to life-threatening coagulopathy requiring specific and immediate therapeutic interventions to prevent mortality and ensuing morbidity due to shock-related hypoperfusion, hypothermia, and acidosis, known as the "lethal triad" of irreversible shock. Recent introduction of the recombinant activated human coagulation factor VII (FVIIa) in the clinical therapy of patients with traumatic coagulopathy might progress to a valuable routine treatment option for patients with severe TBI [133]. To date, administration of FVIIa is a therapy of last resort. Currently, a prospective multicenter study is under way to evaluate effects of routine application in patients with contusions > 5 ml. Upon binding to tissue factor at the site of injury, FVIIa induces a "thrombin burst" on the surface of activated platelets and thereby potentiates fibrin formation. The developing barrier against proteinase inhibitors confines the clot to the site of injury and plugs the bleeding vessel. However, the induced "thrombin burst" might endanger cerebral viability via activation of specific neuronal and glial thrombin receptors. While low concentrations can protect neurons and astrocytes, high doses can become lethal, disrupt the blood-brain barrier and induce edema formation [134]. In a recently published experimental study, continuous infusion of thrombin stressed its neurotoxic potential and ensuing memory impairment [135]. Whether similar toxic thrombin concentrations are reached upon single-dose administration under clinical conditions remains to be determined to possibly assess and monitor adverse effects.

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