

Head, Thoracic, Abdominal, and Vascular Injuries

Trauma Surgery I

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Intensive Care Treatment Options of Elevated Intracranial Pressure Following Severe Traumatic Brain Injury

2

John F. Stover and Reto Stocker

Abbreviations

ADH	Antidiuretic hormone	NSE	Neuron specific enolase
ADP	Adenosine diphosphate	OER	Oxygen extraction ratio
AEP	Acoustic evoked potentials	OGI	Oxygen-to-glucose index
ALI	Acute lung injury	paO ₂	Partial arterial oxygen pressure
APOE	Apolipoprotein E	paCO ₂	Partial arterial carbon dioxide pressure
ARDS	Adult respiratory distress syndrome	PARP	Poly ADP ribose polymerase
ATP	Adenosine triphosphate	PET	Positron emission tomography
BGA	Blood gas analysis	PEEP	Positive endexpiratory pressure
BIS	Bispectral index	ptiO ₂	Partial pressure tissue oxygenation
CPP	Cerebral perfusion pressure	ScvO ₂	Central venous oxygen saturation
CSD	Cortical spreading depression	SEP	Sensory evoked potentials
CSF	Cerebrospinal fluid	SIADH	Syndrome of inappropriate antidiuretic hormone secretion
CSW	Cerebral salt wasting	SjvO ₂	Jugular venous oxygen saturation
CT	Computerized tomography	SPECT	Single photon emission computed tomography
CYP	Cytochrome P	SVR	Systemic vascular resistance
DIC	Disseminated intravascular coagulopathy	TCD	Transcranial Doppler sonography
ECG	Electrocardiogram		
EEG	Electroencephalogram		
EVD	External ventricular drainage		
GABA	gamma aminobutyric acid		
GCS	Glasgow Coma Scale		
GFAP	Glial fibrillary acidic protein		
ICP	Intracranial pressure		
I/E	Inspiratory to expiratory ratio		
LGI	Lactate-to-glucose index		
LOI	Lactate-to-oxygen index		
MABP	Mean arterial blood pressure		
MRI	Magnetic resonance imaging		
NaCl	sodium chloride		

2.1 Summary

The intensive care treatment of patients with severe traumatic brain injury (TBI) must consider local alterations as well as systemic influences. This, in turn, requires broad clinical experience and knowledge to see and comprehend these severely injured patients in their entirety. This not only pertains to patients with additional injuries but is also valid for patients with isolated severe TBI. Only then can we practice a brain-oriented therapy. A merely brain-centered therapy carries the risk of inducing extracerebral organ injuries.

The main focus of our attention is to prevent secondary damage, which implies active search and identification of secondary insults. In addition, this forces us to conduct a preemptive and – if required – aggressive strategy. Apart from our clinical judgment we

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must rely on specific cerebral and systemic monitoring tools which allow us to make sensible therapeutic decisions and to also adapt the type and extent of the different therapeutic interventions according to dynamic changes over time. Only then can we reduce the risks of damage induced by the well-meaning therapeutic interventions.

To date we do not possess a simple, easy-to-use, and widely accepted concept with which all patients with their different traumatic lesions and individual courses could be treated identically. Even the classical and much cited works, i.e., the “Rosner concept” and the “Lund concept,” can actually only be applied to small proportions of the TBI population as investigated in the original works. These descriptions were never corroborated in prospective, randomized, placebo-controlled trials, which, of course, would subject us to a tremendous ethical burden.

The large mistake lies within the academic attempt of (over)simplifying complex and difficult-to-understand pathophysiologic and pharmacologic interactions with the aim of generating broad knowledge. This, of course, results in a loss of important and decisive pieces of information which falsely declare the “Rosner concept” as a hyperdynamic and hypervolemic treatment option to modulate cerebral perfusion pressure (CPP) and by which the “Lund-concept” is misunderstood as a categoric and inflexible reduction in CPP to 50 mmHg in all TBI patients.

Based on the pathophysiologic changes, the interacting cascades, and the differential pharmacological and therapeutic influences, we are forced to search for individualized treatment options which allow more flexible adaptation of the different treatment options over time. Thus, it is conceivable that we must combine integral parts of different pathophysiologically – and pharmacologically – driven concepts.

In the following chapters we will elaborate on certain principles which allow improving the treatment of patients with severe TBI. Concomitantly certain procedures and interventions must be categorically practiced, e.g., administration of oxygen including safety intubation, controlled ventilation, stabilization of the arterial blood pressure, and adequate analgesia and sedation, to avoid inducing secondary insults at *any* time point.

The reader is reminded that in-depth and specialized clinical experience cannot be substituted by this chapter but it surely can be broadened.

2.2 Introduction

Severe TBI is characterized by its complexity and the difficulty in precisely predicting occult secondary alterations which can lead to a progression of the existing brain damage. In this context, the secondary increase of space-occupying lesions such as extra- and intracranial hemorrhages (epidural, subdural hematomas, and contusions) and the progressive growth of brain edema are mediated by activated cascades and simultaneously promote activation of new destructive cascades. The increase in volume (hemorrhages and edema) induces a local and then a global increase in intracranial pressure (ICP). The resulting local as well as global compression of the brain with subsequent impairment of cerebral microcirculation will involve progression of ischemia to local infarcts and thus aggravate preexisting injury and also induce new structural and functional damage. These additional injuries are subsumed as secondary brain damage which stereotypically follow the primary injury and determine survival per se and most importantly quality of individual survival (Fig. 2.1).

While the primary damage cannot be influenced any more it is our interdisciplinary duty to prevent secondary growth and aggravation of the present damage

Traumatic brain injury: dynamic continuum

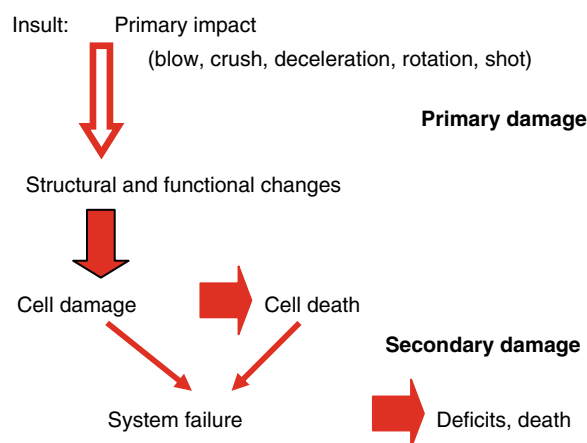


Fig. 2.1 Schematic drawing of dynamic cascades activated by a defined primary lesion which can progress to a larger lesion over time. This secondary brain damage can be influenced by other pathologic forces. In the worst case, these alterations can induce irreversible damage and ultimately result in death of these patients

and to avoid induction of new injuries. This, however, requires specialized knowledge, and continuous and active search of different secondary brain insults. These secondary insults, in turn, can only be treated aggressively if they are sought for aggressively in daily clinical routine.

For this we cannot only rely on our theoretical knowledge but we must also incorporate different monitoring techniques to unmask otherwise occult alterations.

While the arising problem of space-occupying and ICP-increasing hematomas is solved relatively easily by surgical evacuation, treatment of vasogenic and cytotoxic edema is far more cumbersome since all investigated anti-edematous drugs which provided promising results in preclinical experimental studies failed in clinical investigations. Apart from species- and model-related issues influences of different treatment modalities differing between centers must also be considered. Furthermore, we lack clear evidence-based data regarding benefit and potential deleterious effects of contemporary treatment options and modalities which are strongly influenced by our personal conviction.

Within the scope of this chapter we will characterize different nonsurgical possibilities aimed at treating elevated ICP following severe TBI. In this context, prevention and treatment of secondary brain damage are mutually dependent and show a reciprocal influence.

2.3 Pathophysiologic Basis

2.3.1 Local Autodestructive Cascades and Local Secondary Insults

The structural and functional injuries encountered following severe TBI are influenced by a plethora of different pathophysiologic cascades which are activated in parallel and sequentially. In principle, these cascades involve alterations within the extra- and intracellular space: activated enzymes (e.g., caspases, metalloproteinases, poly ADP ribose polymerase (PARP)), disturbed perfusion and microcirculation, metabolic impairment due to energetic deficit and mitochondrial dysfunction, excessive and uncontrolled neuronal excitation, excessive glial activation, activated inflammatory reactions, production of free oxygen radicals with concomitant

impaired antioxidative compensation. In addition, activation of transcription factors which may aggravate DNA damage (e.g., c-fos, c-jun), reduce DNA injury (e.g., bcl-2, p53), or mediate both beneficial as well as damaging effects (e.g., PARP) have been identified [1]. These different damaging processes are expanded by a certain genetic predisposition (e.g., APOE ϵ 4 associated with posttraumatic dementia) [2, 3]. These activated processes contribute to apoptotic and necrotic alterations with their detailed regulatory processes and pharmacologic targets currently being characterized [4]. The different cascades are characterized by a heterogeneous regional and temporal profile and consist of progressive injury of different cellular compartments:

- Endothelial cells with activation of inflammatory cascades, development of local microthrombi, vasoconstriction and vasodilation;
- Cell membrane with transport proteins and disturbance of electrolyte homeostasis;
- Cytosol with enzymes and production of different pro-inflammatory cytokines and destructive free oxygen radicals;
- Endoplasmic reticulum with disturbed calcium homeostasis;
- Mitochondria with impaired oxidative phosphorylation and reduced ATP synthesis.

In addition, different cellular compartments are disturbed functionally (neurons \leftrightarrow glia \leftrightarrow endothelial cells), which results in disturbed autoregulation, a progressive energetic deficit as a harbinger of ensuing ischemia in terms of cortical spreading depression (CSD), as well as a disturbed balance between excitatory and inhibitory transmitters with subsequent excitotoxicity and/or prolonged coma (Table 2.1).

As revealed by animal experiments, these signs of secondary functional and structural deterioration develop under otherwise stable conditions with sufficient cerebral perfusion as well as adequate oxygenation, normothermia, and normocapnia. These alterations can be aggravated by systemic secondary insults. This stresses the necessity of preventing additional insults to avoid aggravation of the processes which stereotypically evolve during the early posttraumatic phase.

While processes confined to the intracellular compartment remain occult at the bedside and can only be determined histologically, changes within the extracellular space and later on in the cerebrospinal fluid (CSF)

Table 2.1 Local secondary insults

Secondary insult	Causes	Consequences	Time point	Treatment
EEG activity	Neuronal activation	Energetic deficit Brain edema, ICP↑	Always	Analgesia, sedation Hypothermia
Ischemia	Microthrombus Compression	Infarct, brain edema, ICP↑	Always	Increase CPP, administer volume
Hyperemia	Disturbed autoregulation Excessive dilatation Impaired constriction	Brain edema, ICP↑	Always	Hyperventilation Controlled CPP reduction <i>CAVE</i> : increased ICP due to vasodilation resulting from decreased CPP
Vasospasm	Disturbed autoregulation Impaired dilatation Excessive constriction	Brain edema, ICP↑	Always	Hypoventilation Controlled CPP increase
Cortical spreading depression	Functional impair- ment: neurons, astrocytes	Ischemia, brain edema, ICP↑	Always	Maintain blood glucose > 5 mM, upper limit is currently under debate Barbiturates
Coagulopathy	Thrombus formation Fibrinolyse	Ischemia/infarct Hemorrhage	Early phase	Correct systemic coagulation parameters
Inflammation/ infections	Ventriculitis Meningitis Abscess	Hydrocephalus, ICP↑ Seizures	Late phase	Antibiotics, removal of ventricular drainage/shunt Excision

and blood can unmask previous events. For this, modern intensive care medicine uses different invasive and noninvasive techniques. These are described in detail in (see Sect. 2.4).

2.3.2 Systemic Secondary Insults

Apart from local processes, systemic changes are also of pathophysiologic relevance as they are known to influence brain edema formation (Table 2.2).

The classical secondary insults which increase mortality and morbidity are arterial *hypotension*, *hypoxia* [5], and uncontrolled (prophylactic) *hyperventilation* [6]. Insufficient cerebral perfusion and oxygenation of the already injured brain and excessive vasoconstriction with subsequent local and global perfusion and impaired metabolic supply are the leading characteristics of these secondary insults.

Further secondary insults are *fever* with cerebral vasodilation [7], and systemic inflammation due to infectious processes (e.g., pneumonia) with additional activation of local destructive cascades. Sepsis, in turn,

with its detrimental hypotension and coagulopathy, can induce multiorgan failure, thereby resulting in hypotension and hypoxia, which will increase secondary brain damage. In addition, fast and uncontrolled rewarming of hypothermic patients will induce systemic vasodilation with subsequent impaired cerebral perfusion and disturbed cerebral autoregulation. This, in turn, increases the risk for ICP, raising hyperemia.

Anemia with a hematocrit <24% due to active bleeding, insufficient transfusions, excessive volume administration, and reduced production and effect of erythropoietin will impair cerebral oxygen supply of the injured brain, thereby promoting edema progression and ICP elevation, explaining the increased mortality and rate of complications [8].

Excessive activation of the coagulation cascade with an imbalance between activation and inhibition of activated cascades can result in *coagulopathy*, which unfortunately is not obvious clinically. Excessive fluid administration is feared for inducing *dilution coagulopathy*. Liberation of tissue plasminogen activator (t-PA) highly concentrated within the brain maintains activation of the coagulation cascade resulting in a loss of various coagulation factors, e.g., factor XIII. This,

Table 2.2 Systemic secondary insults

Secondary insult	Causes	Consequences	Time point	Treatment
Hypotension	Hypovolemia Cardiodepression Warming Fever	Reduced perfusion → Ischemia → Infarct Brain edema, ICP↑	Always	Volume infusion Vasopressors, inotropics Slow warming Treat fever
Hypoxia	Pulmonary pathology	Cell damage Brain edema, ICP↑	Always	Adapt ventilatory settings (FiO ₂ , PEEP, I/E, Tidal volume)
Fever	Central, infection	Brain edema, ICP↑	Always	pharmacologic, physical cooling
Hyperglycemia	Stress, nutrition	Brain edema, ICP↑	Always	Insulin
Hypoglycemia	Nutrition, insulin	Brain edema, ICP↑	Always	Adapt nutrition, maybe controlled glucose infusion
Hypernatremia	Diabetes insipidus Hyperaldosteronism Iatrogenic	Brain edema, ICP↑, Pontine myelinolysis	Early phase	Desmopressin, <i>CAVE</i> : long half-life, difficult to guide Maybe: aldosteron antagonists, <i>CAVE</i> : difficult to guide Volume infusion
Hyponatremia	SIADH, CSW, iatrogenic Hypoaldosteronism, diuretics	Brain edema, ICP↑	Late phase	Fludrocortison, <i>CAVE</i> : difficult to guide Reduce or increase volume infusion
Coagulopathy	Activated coagulation Increased consumption of factors Reduced synthesis Dilution Consumption of platelets	New hemorrhages Increased volume of existing hemorrhages Brain edema, ICP↑	Early phase	Substitution of factors, including factor XIII and fibrinogen, administration of vitamin K, platelets, and normalize ionized calcium
Anemia	Uncontrolled hemorrhages dilution	Hypoxemia Brain edema Brain edema, ICP↑	Early phase	Transfusion
Hyperammonemia	Disturbed hepatic function (genetic, pharmacologic: antiepileptics, barbiturates, altered intestinal flora, increased protein administration)	Brain edema, ICP↑	Late phase	Change nutrition: reduce amount of protein; dialysis, avoid valproic acid

in turn, promotes faster lysis of already formed thrombi. Consequently, an increase in volume of existing hemorrhages or generation of new hemorrhages [9] will increase ICP and promote progression of brain edema. In conjunction with the activated coagulation cascade platelets are used, thereby resulting in *thrombocytopenia* and functional disturbance of circulating platelets [10], which are aggravated by preexisting endocrinologic illnesses and pharmacologic-induced thrombocytopathies (e.g., renal insufficiency, platelet aggregation inhibitors). These alterations support damaging intracranial and intracerebral hemorrhages.

Disseminated intravascular coagulopathy (DIC) as well as platelet loss and platelet dysfunction promote severe blood loss in case of additional injuries, which, in turn, increases the risk of hypotension and ischemia, and hypoxia in all organ systems.

Manifest blood glucose deviations in terms of *hyper- and hypoglycemia* (i.e., above 10 and below 5 mmol/L) as well as strong undulations are of pathophysiologic importance. In this context, hyperglycemia activates local inflammatory processes which are associated with a sustained rate of multiorgan failure and increased mortality [11]. Hypoglycemic episodes aggravate the

generation of progredient functional disturbances in terms of CSD [12].

Strong and mainly fast decreases in blood sodium levels are feared for their edema-promoting effect and limited therapeutic options [13]. In this context, *hyponatremia* (<120 mmol/L) due to excessive release of antidiuretic hormone ADH (SIADH, Schwarz-Bartter syndrome) or release of natriuretic peptides (cerebral salt wasting (CSW)) can promote brain edema formation and reduce the threshold for seizures. A relative adrenal insufficiency with subsequent hypoaldosteronism resulting from previous administration of etomidate, usually for intubation [14], deep sedation [15], or within the context of sepsis [16], will induce hyponatremia. Initially *hypernatremia* reduces edema formation. However, within 3 days of constant hypernatremia it automatically induces compensatory uptake of osmotic active substances, so-called osmolytes, i.e., mainly amino acids, to normalize intracellular volume and cell membrane tension [17]. A later decrease in blood sodium will result in a relative increase of the intracellularly trapped osmolytes expanding their osmotic strength. This, in turn, will cause a strong increase in intracellular edema formation with a subsequent potentially lethal increase in ICP. Hypernatremia during the early phase can result from a loss in ADH due to pituitary ischemia, a sign of functional herniation. Hypernatremia developing later on could result from excessive infusion of sodium-containing solutions or liberal administration of diuretics with subsequent hypovolemia. Hormonal changes with typical lab signs of a hyperaldosteronism are also encountered.

Rare cases of *hyperammonemia* must be actively searched for. Due to its high solubility, lipophilicity, and diffusion properties ammonia easily penetrates the brain where it induces intracellular water accumulation related to enzymatic compensatory and detoxification processes mainly involving glutamate and glutamine. Increased neuronal excitation also plays an important role. The evolving brain edema results in an increase in ICP, which in a worst case scenario can end in lethal brain stem herniation [18, 19]. Apart from the real hyperammonemia we must consider a laboratory artifact resulting from concomitantly increased blood gamma-glutamyl transpeptidase (GGT) levels as elevated GGT induces an enzymatic release of ammonium predominantly from glutamate which is measured as ammonia, thus resulting in artificially

elevated blood ammonia concentrations. Apart from a genetic predisposition which is rather rare in adults and predominantly determined in children, pharmacological influences in combination with exhausted enzymes and co-enzymes of the urea cycle and/or excessive uptake of protein stemming from enteral and/or parenteral nutrition are discussed as potential inductors of hyperammonemia. The classical drugs known to induce hyperammonemia are antiepileptics, barbiturates, and volatile anesthetics which can mutually perpetuate their hyperammonemia-inducing properties. In addition, change in intestinal bacteria resulting in increased production of ammonia must be considered.

In general, this hyperammonemia is reversible, provided it is identified in time. However, it is of utmost importance to measure blood ammonia in regular intervals or whenever an increase in ICP cannot be explained otherwise. Only then can we decrease mortality and reduce additional brain damage if adequate interventions are started at blood ammonia levels exceeding 50 $\mu\text{mol/L}$.

On a therapeutic basis production of ammonia must be reduced and circulating ammonia must be removed. Production of ammonia is decreased by enteral administration of lactulosis or changing nutrition solution to a protein-poor or even protein-free solution. In rare cases, other compounds, such as arginine, sodium benzoate, sodium phenylbutyrate, or L-carnitine, must be tried. In cases of elevated ICP and blood ammonia levels exceeding 100 $\mu\text{mol/L}$ hemodialysis must be begun immediately.

These different systemic secondary insults must be prevented in modern intensive care.

2.3.2.1 Crucial Points and Pearls

- The primary brain damage is followed by a stereotypical increase during the first 24–48 h and is considered as secondary brain damage.
- The different destructive cascades are aggravated by local and systemic secondary insults which enlarge the secondary brain damage.
- Systemic secondary insults can develop at any time and must be corrected to prevent progression of the secondary brain damage.
- Systemic secondary insults, i.e., hypotension, hypoxia, hyperventilation, anemia, fever, hypo-/hyperglycemia,

hypo-/hypernatremia, coagulopathy/thrombocytopenia, hyperammonemia, must be sought for actively so they can be prevented and corrected adequately.

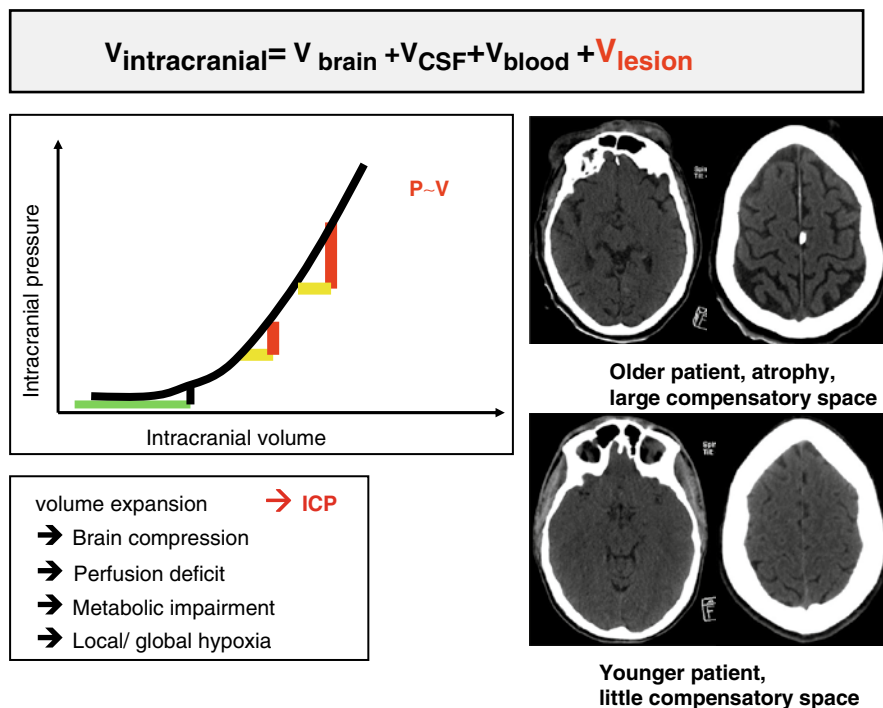
2.3.3 Increase in Intracranial Volume and Intracranial Pressure

As already described in 1823 by Monro and Kelly the simple concept of the pathophysiologic interrelationship of intracranial volume and pressure continues to be of clinical relevance even in contemporary neurotraumatology. The basis for the Monro–Kelly doctrine is formed by the anatomic boundaries consisting of the inflexible skull bones and the different partial volumes defined by the brain: approx. 85%, CSF: approx. 5–15%, and intracranial blood volume: approx. 5–10%. Under normal conditions these different partial volumes result in a total volume which is maintained constant by a compensatory adaption of the different partial volumes. In this context an increase in intracranial blood volume is observed in cases of vasodilation (hyperemia), and CSF is moved from the cranial space to the spinal compartment. In

case the total volume cannot be maintained constant or the compensatory mechanisms have been exploited, then any additional increase in volume will elevate ICP. Under pathologic conditions the net volume is increased by various intracranial lesions, which will decrease the compensatory shifts of the physiologic partial volumes (Fig. 2.2). In this context, the age of the patient is decisive. While younger brains nearly completely fill the intracranial space and are limited by a reduced elasticity with an increased resistance, older brains are characterized by the opposite characteristics. This explains why older patients with preexisting global atrophy and reduced resistance can tolerate larger volumes for a longer period of time before they suffer from clinical worsening and require neurosurgery.

Following severe TBI, space-occupying processes (hemorrhages, contusion, brain edema) and their additional increase in volume result in a faster exhaustion of the physiologic compensatory mechanisms. As a consequence an increase in volume which normally is tolerated well results in disproportionately elevated ICP. This increase in pressure, in turn, induces new and progressing secondary damage which can induce and maintain a vicious circle [20].

Fig. 2.2 Schematic drawing of the relationship of intracranial volume and intracranial pressure (ICP) (Monroe–Kelly doctrine) and possible pathophysiologic cascades which can result in secondary brain damage. The included computed tomography (CT) pictures illustrate the influence of underlying brain volume on the increase in ICP whenever total intracranial volume cannot be maintained constant. In cases of brain atrophy larger lesion volumes can be compensated longer before ICP increases. In brains with less atrophy, i.e., younger patients, already small lesions can induce a faster and more severe increase in ICP



Progressive increases in volume and pressure result from intracranial hemorrhages, contusions, focal and global brain edema, vasodilation with expansion of the intracranial blood volume, and vasospasm with ischemia-induced brain edema formation. Occasionally, disturbed CSF circulation with resulting hydrocephalus (due to lower herniation and occlusion of the aqueduct) and venous infarcts is caused by sinus vein thrombosis (due to fractures in the vicinity of the jugular venous bulb or skull fractures close to the sigmoid/transverse/confluens sinus). In addition, the rare but important and devastating traumatic lesion to the internal carotid artery including its dissection must be remembered, which can result in a fulminant hemispheric edema formation. An inadequate positioning of the patient (too flat or too steep) can impair the venous outflow, which, in turn, will also increase the ICP. Furthermore, a cervical collar as well as a catheter-related formation of a thrombus within the internal jugular vein can also impair cerebral venous outflow.

Apart from intracranial and intracerebral reasons for elevated ICP, an impaired venous outflow due to thoracic and abdominal compartment syndrome must also be considered [21]. These compartment syndromes can result from uncontrolled volume administration or a combination of gastrointestinal paralysis caused by deep analgesia and sedation, immobilization, enteral/parenteral nutrition, hypothermia, and the generalized edema formation related to inflammatory-induced capillary leakage. Under certain circumstances a laparotomy becomes inevitable.

2.3.3.1 Crucial Points and Pearls

- Elevated ICP depends on the intracranial volume expansion, distribution of different physiologic and pathologic volumes (brain, CSF, blood, lesions), elasticity, and size of the brain.
- The volume-dependent ICP increasing effect is dynamic, i.e., the same volume expansion at different time points will result in different extents of elevated ICP and intracranial hypertension (ICP > 25 mmHg).
- The exact reason for an increase in ICP must be identified. Only then can an adequate treatment be initiated.
- Apart from intracranial and intracerebral causes we must also search for systemic reasons such as

impaired venous outflow in case of thoracic and abdominal compartment syndromes.

2.4 Neuromonitoring

To obtain an in-depth insight in otherwise occult changes and thus guide differentiated therapeutic interventions in an intelligent manner, different and supplementary noninvasive and invasive monitoring methods must be combined and integrated in daily routine (Table 2.3). Based on data obtained from animal experiments and the finding that hemorrhages and contusions exhibit a stereotypic growth pattern during the first days under experimental and clinical conditions (Fig. 2.3) specific neuromonitoring must already be used early after TBI, and also during phases with normal ICP values below 15 mmHg. Only then can we unmask pathologic processes early on. This, in turn, is essential to win time for appropriate and correcting interventions before ICP increases and before secondary brain damage progresses. The difficulty, however, is to identify those patients requiring aggressive and invasive surveillance in whom the initial computed tomography (CT) does not exhibit obvious pathologic findings. It is important to bear in mind that diffuse axonal injuries cannot be seen in the initial CT scan and that certain lesions require at least 2–6 h to develop. This is of importance if the initial CT scan is obtained within 2 h in clinically comatose patients whose coma cannot be explained by other reasons such as alcohol, seizure, or hypothermia. Careful evaluation of their trauma history and consideration of the time point when the initial CT scan was performed must be integrated in our decision making. Especially in cases of high-speed accidents and falls with additional injuries an increased risk for hemorrhages and coagulopathy must be considered. Thus, control CT scans should be performed in tight intervals, especially if the patients require surgical procedures and anesthesia/sedation does not allow adequate neurological evaluation. In the presence of pathologic alterations patients should be submitted to a standardized intensive care treatment protocol for at least the first 24 h aimed at preventing progression of secondary brain damage. This protocol should include insertion of an ICP probe.

Table 2.3 shows different monitoring methods with their implications, advantages, and disadvantages.

Table 2.3 Neuromonitoring: areas of interest, implications, advantages, disadvantages

Monitoring	Area of interest	Implications	Advantages	Disadvantages
ICP	Focal/global	Increase in intracranial volume and pressure	Adapt therapeutic interventions	Normal values ¹ physiology
EEG	Global	Guide sedation Assess seizure activity	Topographic analysis	Requires special knowledge
BIS EEG	Frontal/global	Guide sedation	Easy to use	No topographic analysis
SjvO ₂	Global	Guide CPP, paCO ₂	Continuous (if oximetry works)	Discontinuous, requires BGA
ptiO ₂	Focal	Guide CPP, paCO ₂ , transfusion threshold	Continuous	Invasive
Microdialysis	Focal	Guide CPP, paCO ₂ , sedation	Metabolic monitoring	Expensive, difficult to interpret
TCD	Focal	Guide CPP, paCO ₂	Easy, reproducible	Discontinuous, requires expertise
Imaging	Focal/global	Indication for surgery, guide therapy	Visualization of lesions, metabolic alterations	Time-consuming, difficult to perform in unstable patients, specialized centers
Autoregulation	Focal/global	Guide CPP, paCO ₂ , sedation	Noninvasive (ICP, MABP, TCD)	Specialized software

2.4.1 ICP and Compliance

The continuous measurement of ICP was introduced in clinical routine in the 1970s. Following its initial euphoria, ICP was regarded as the primary parameter to unmask pathologic intracranial processes and to explain the high mortality and morbidity observed 30–50 years ago. The general view that an increased ICP is always pathologic led to the widely distributed misconception that a normal ICP value is equal to absence of pathologic processes. This, however, is a fallacy. New data convincingly show that metabolic alterations precede increases in ICP [22]. This, however, can only be seen if the appropriate monitoring is used.

Apart from assessing an increase in ICP, measured ICP allows to calculate the CPP ($CPP = MABP - ICP$), which is an indirect measure for global cerebral perfusion and which forms the basis for further therapeutic decisions.

The ICP level of 20–25 mmHg is considered pathologic as mortality was significantly increased at ICP levels exceeding 20 mmHg [23]. However, this threshold stems from a time of insufficient monitoring of parameters which have been integrated in modern intensive care following severe TBI, e.g., jugular venous oxygen saturation (SjvO₂), partial pressure tissue oxygenation (ptiO₂), microdialysis, or transcranial

Doppler sonography (TCD). Strictly adhering to this threshold implies missing an early start of specific interventions, which confounds neuroprotection of various therapeutic interventions. Already in 1982 Saul and Ducker were able to show a significantly reduced mortality at an ICP threshold of 15 mmHg compared to a historical group of patients in whom ICP was not treated before it had reached 20–25 mmHg: 28% vs. 46% [24]. Unfortunately, the impact of these results is weakened by the use of historic control patients and the fact that there was no follow-up study or a prospective randomized controlled trial. From a methodological and technical point the ICP is influenced by several factors, such as the presence of a craniectomy, the region of insertion, and measurement, which are important when interpreting the obtained values (Table 2.4). Following a craniectomy including dural expansion we regularly measure low and even negative ICP values until the brain has expanded into the newly generated space. A similar finding is encountered in patients with entrapped air in the subdural compartment which hampers the correct transmission of pressure values. Thus, falsely low and even negative ICP values are measured until the air has been absorbed. The same holds true for parenchymal probes which are positioned within the extraparenchymal space.

Under these circumstances these “false” ICP values mimic normality and trick us into missing pathologic

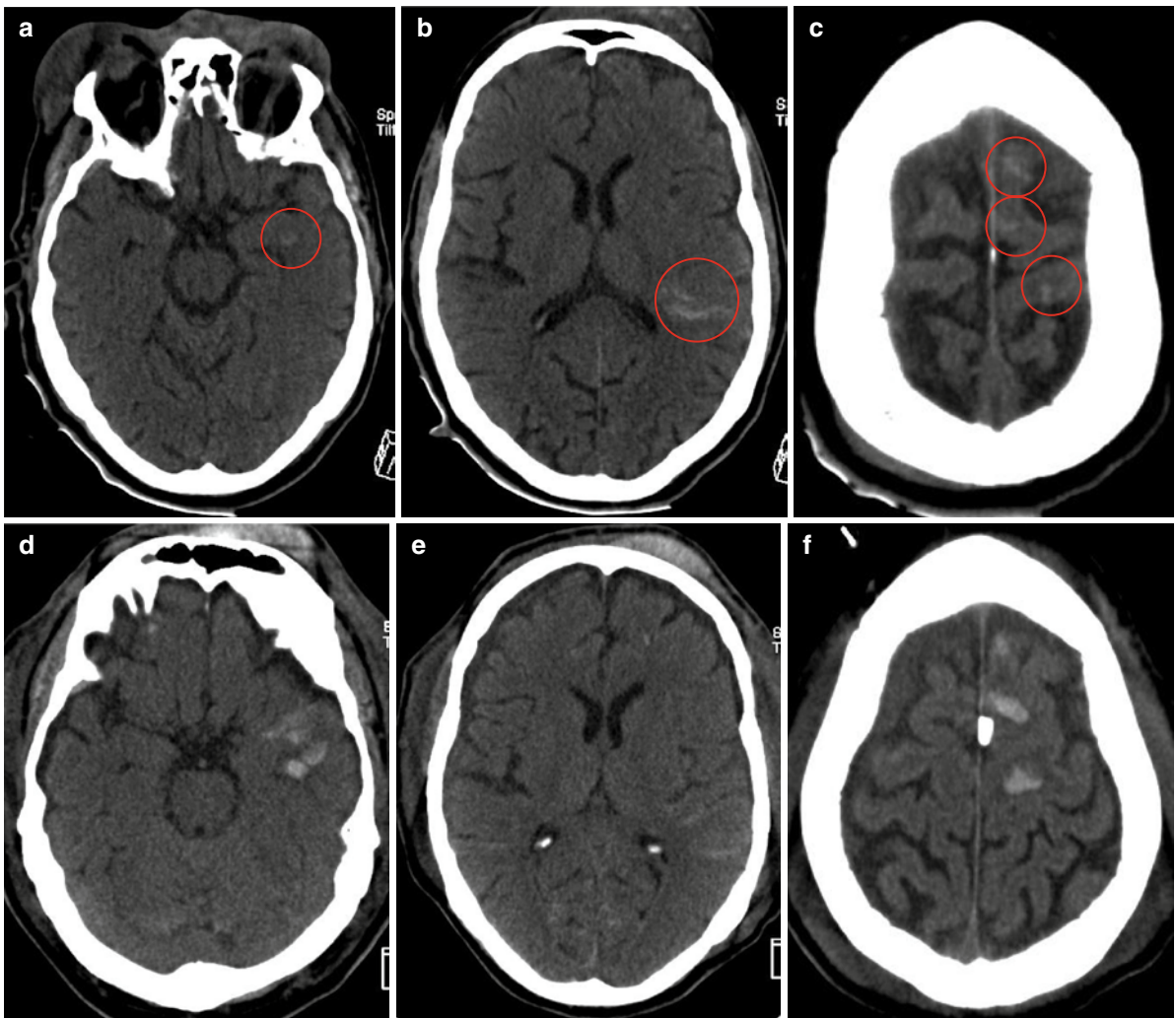


Fig. 2.3 Illustrative example of dynamic changes of different traumatic lesions within the first 24 h. While trying to secure his cat from the roof a patient fell from a height of 7 m. He suffered from severe traumatic brain injury (TBI) and severe abdominal injury and long bone fractures. While only small lesions were seen in the initial computed tomography (CT) scan (marked with red circles) performed 2 h after injury ((a) left temporal contusion,

(b) left parietal traumatic subarachnoid hemorrhage, (c) left frontal contusions), the contusions significantly increased (within the first 24 hrs.) in size ((d and f)). At the same time, traumatic subarachnoid hemorrhage resolved (e). The increase in contusion volume occurred despite intact and normal plasmatic and thrombocytic coagulation

alterations as we do not actively search for otherwise occult signs of evolving brain damage. This enforces the concomitant application of several monitoring methods to allow an internal control and to minimize the risk of missing pathologic changes.

Earlier clinical studies clearly showed that different pressure values and pressure gradients exist within the supratentorial compartment. These pressure gradients are influenced by space-occupying lesions with a lesion >25 mL and a midline shift >3 mm and are only unmasked if several ICP probes are used [25]. Thus,

from a puristic standpoint we must question the validity and correctness of the decisions and therapeutic interventions when only using one ICP probe as we miss the presence of regionally differing pressure values. As a consequence, some areas of the injured brain tend to be over- or undertreated. The complexity of this problem is increased by the regional and temporal heterogeneity of pathologic changes. Based on the presence of these pressure compartments it is recommended to insert the ICP probe on the side with the predominant space-occupying lesion, to obtain a more

Table 2.4 ICP probes, advantages and disadvantages

ICP probe	Area of insertion	Advantages	Disadvantages
Parenchymal probe	Parenchyma	Independent of the ventricular system	Trephination
Ventricular drainage	Ventricular system	Independent of local pressure gradients Release of CSF to decreased ICP	Requires accessible ventricular system Risk of damaging basal ganglia Risk of infections Excessive production of CSF following CSF drainage
Subdural probe	Beneath the dura	No tissue damage	Risk of damaging bridging veins Entrapped subdural air impairs pressure conductance causing strong deviations
Epidural probe obsolete	Outside the dura	No tissue damage	Strong deviations

appropriate CPP. In clinical practice, however, the location and extent of the different lesions are decisive. In this context, some neurosurgeons fear causing severe damage by inserting the ICP probe in the frontal lobe of the left hemisphere assuming this is the dominant hemisphere. Furthermore, insertion of an ICP probe into an existing contusion increases the risk of additional hemorrhage and growth of the contusion. This risk can be minimized by inserting the ICP probe in the contralateral pressure-receiving side.

The least pressure differences are found within the ventricular system, provided the catheters are inserted correctly. To minimize artifacts parenchymal probes are superior to sub-epidural and epidural probes and thus should be favored. Specialized ICP probes inserted in the ventricular system also allow draining of CSF to reduce elevated ICP. CSF drainage, however, is only possible if the ventricular system is accessible and it is not compressed, for example, by progressive generalized brain edema. Thus, external ventricular drainage (EVD) can only be used in a small proportion of patients. Furthermore, the increased risk of ventriculitis compromises the benefit of the EVD.

In an attempt to gain more insight into intracranial pathology, to find an early warning system for ensuing compromised intracranial compensatory mechanisms, and to better unmask dynamic ICP changes, intracranial compliance was investigated. For this, a special catheter equipped with a balloon is inserted in the ventricular system. Standardized volume expansion of the balloon increases ICP, which, in turn, allows calculating resistance and compliance of the intracranial compartment. However, due to poor data quality and the missing predictability of ensuing ICP increases and hypoxic

episodes this technique cannot be recommended for daily clinical routine [26].

A regular ICP curve consists of three peaks which reflect the pressure profile determined in a normal arterial pressure curve. Providing good quality of the ICP curve that changes within the pressure profile allows prediction of disturbance in cerebral autoregulation. While normally the first peak is the highest, the second peak exceeds the first peak in case of disturbed cerebral autoregulation. This results from an absent or inadequate vasoconstriction in response to the arterial pressure wave which expands the diameter of the arteries. This curve pattern can precede the evolving increase in ICP within the following 12 h due to excessive cerebral vasodilation (Fig. 2.4).

Apart from this bedside and simple ICP curve interpretation more refined and mathematically sophisticated analysis of the ICP curve by concomitantly considering changes in arterial blood pressure and continuously assessing changes in flow velocity of the middle cerebral artery (MCA) can be performed. This continuous functional analysis of pressure reactivity reflects pathophysiologic alterations almost in real time and allows differentiating patients with severe functional disturbances and worse outcomes compared to those with reduced mortality and morbidity [27].

As in any neurosurgical procedure insertion of an ICP probe is associated with the risk of inducing additional brain injury. Special care must be taken to limit the penetration depth to a maximum of 3 cm below the skull line and to safely secure the ICP probe to prevent it from accidentally dislocating and penetrating deeper regions of the brain. Thus, special bolts should be used and mere attachment to the skin should be avoided

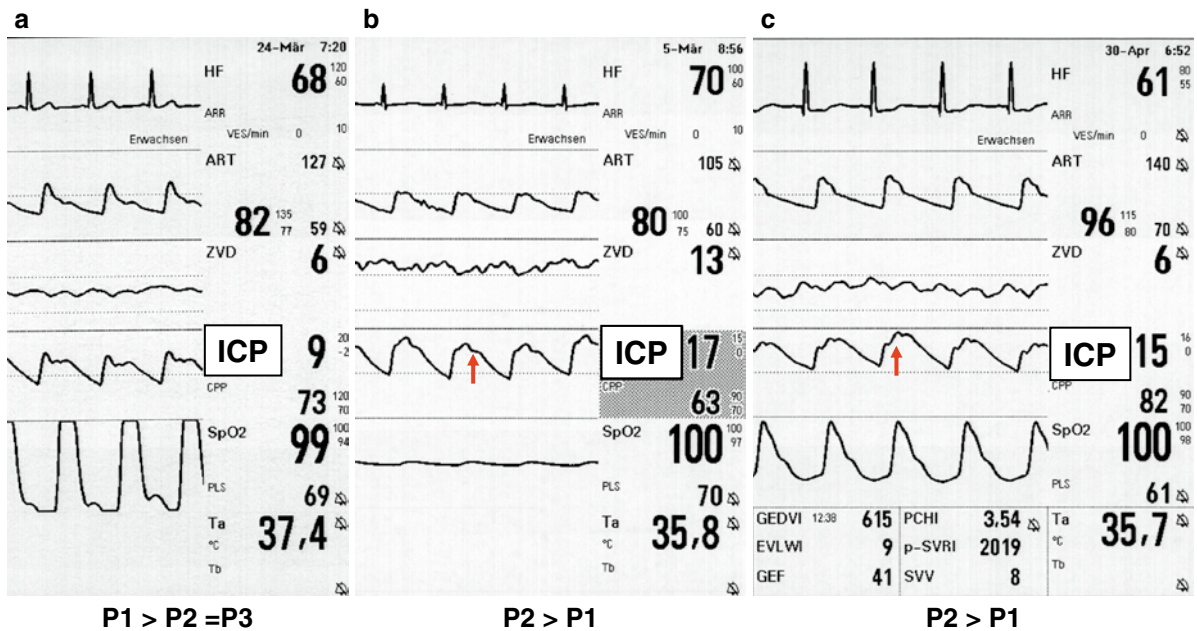


Fig. 2.4 Illustrative examples of curve patterns of the intracranial pressure (ICP) curve, which can be analyzed at the bedside. Under normal conditions, i.e., with adequately reacting cerebral arteries, the ICP curve reflects the three pressure peaks of the arterial pressure curve (a). Here, the first peak is the largest and is followed by two smaller peaks. Under pathologic conditions, i.e., whenever cerebral arteries cannot constrict as a response to the first arterial pressure wave that is transmitted to the cerebral arteries, the second peak of the ICP pressure curve will exceed

the first peak (b and c). This reflects underlying vasodilation and can be used as an early warning signal for subsequent increases in ICP due to progressive cerebral vasodilation and hyperemia. A further increase in cerebral perfusion pressure (CPP) is then required to force cerebral vasoconstriction, which, in turn, will decrease ICP. Thus, this pattern allows to identify optimal CPP. This pattern reflecting disturbed autoregulation can occur several times per hour per day, and can even persist for 1–2 weeks

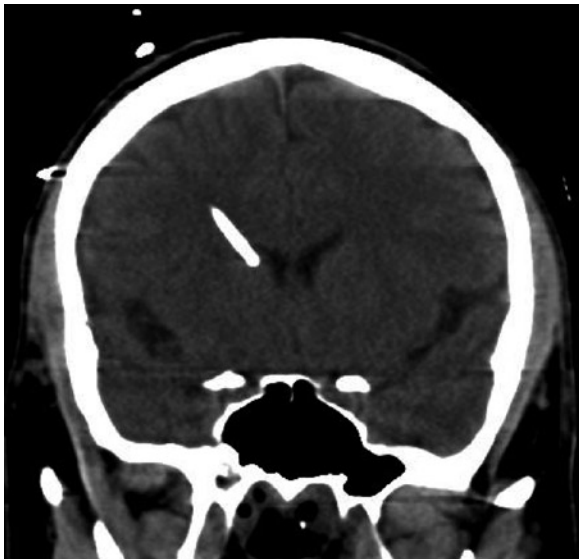


Fig. 2.5 Example of false placement of a parenchymal intracranial pressure (ICP) probe despite using a special bolt: the insertion depth was 6 cm below the skull, nearly penetrating the ventricular system and damaging the caput of the caudate nucleus. The ideal penetration depth is 3 cm below the exterior skull limit

(Figs. 2.5 and 2.6). Special care must also be taken in patients with preexisting frontal hygromas since bridging veins are already under strain and thus can be damaged upon introducing an ICP probe or other monitoring catheters (microdialysis, ptiO_2 , temperature) (Fig. 2.7).

2.4.1.1 Crucial Points and Pearls

- ICP is the primary monitoring parameter following severe TBI.
- A normal ICP <15 mmHg does not guarantee physiologic intracerebral conditions, especially following craniectomy, dura expansion, uncontrolled loss of CSF in case of skull base fractures, or subdural entrapped air, which prevent adequate pressure transmission.
- To date, the general idea is to not escalate therapeutic interventions until ICP exceeds 20 mmHg. This, however, lacks statistically sound evidence. An earlier start, e.g., at 15 mmHg, could reduce stereotypic progression of secondary brain damage.
- With the help of ICP the CPP, an indirect measure of global cerebral perfusion, is calculated.

Fig. 2.6 Example of dislocated parenchymal intracranial pressure (ICP) probe which was not fixed with a bolt system but was merely attached to the skin. The ICP probe was accidentally pushed through the brain during transport from a regional hospital (a) and nearly touched the basal artery (b)

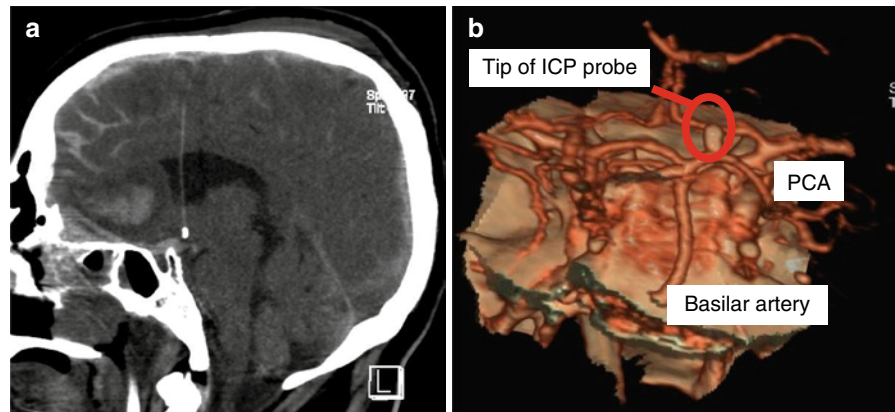
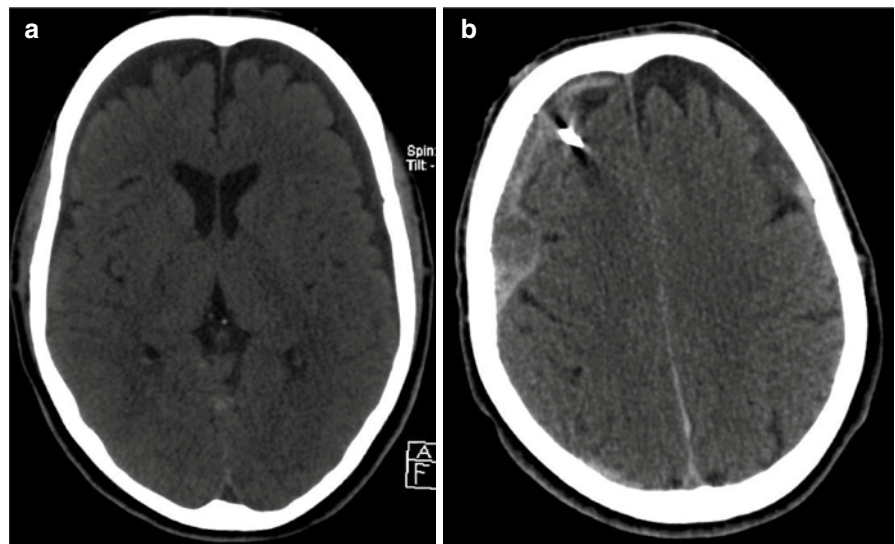


Fig. 2.7 Example of a patient with bifrontal hygroma (a) and induction of an acute subdural hematoma by inserting microdialysis, partial pressure tissue oxygenation (ptiO₂), and temperature probe (b). Special care must be taken in these patients as the bridging veins are under strain due to the existing hygroma. Thus, they can tear easily upon additional manipulation, such as the performed trephination with puncturing of the dura for subsequent insertion of the probes



- Locations and extent of brain lesions as well as the surgical window influence the location of the ICP probe.
- Contemporary practice only includes insertion of one ICP probe, thus missing any pressure gradients and different therapeutic requirements.

2.4.2 Jugular Venous Bulb Catheter: S_{ij}vO₂ and Arterio-Jugular Venous Differences

Guided by ultrasonography to avoid puncturing the carotid artery a single-lumen central venous catheter or alternatively a pediatric pulmonary catheter is inserted in the internal jugular vein. For this, it is of advantage to visualize both internal jugular veins to determine the larger vein. The majority of patients

exhibit a dominant right internal jugular vein while approximately 5% present with a dominant left internal jugular vein. Approximately 10% exhibit comparable bilateral vessel diameters. If possible, the jugular venous catheter should be inserted ipsilateral to the predominantly injured hemisphere [28]. To avoid development of a sinus vein thrombosis caused by prolonged disturbance of the cerebral venous outflow the tip of the catheter should project between approximately 1 cm below the mastoid process and the lower rim of the internal acoustic meatus in a conventional lateral skull/cervical spine X-ray (Fig. 2.8a). It is important to verify the position of the catheter rapidly (within 1 h) after its insertion to minimize the risk of a thrombus formation within the sinus. In case the tip of the catheter cannot be adequately visualized the profile of the catheter itself can help in assessing if the catheter has been advanced too far: whenever a bow is seen in the proximal part (close to the skull base) it means

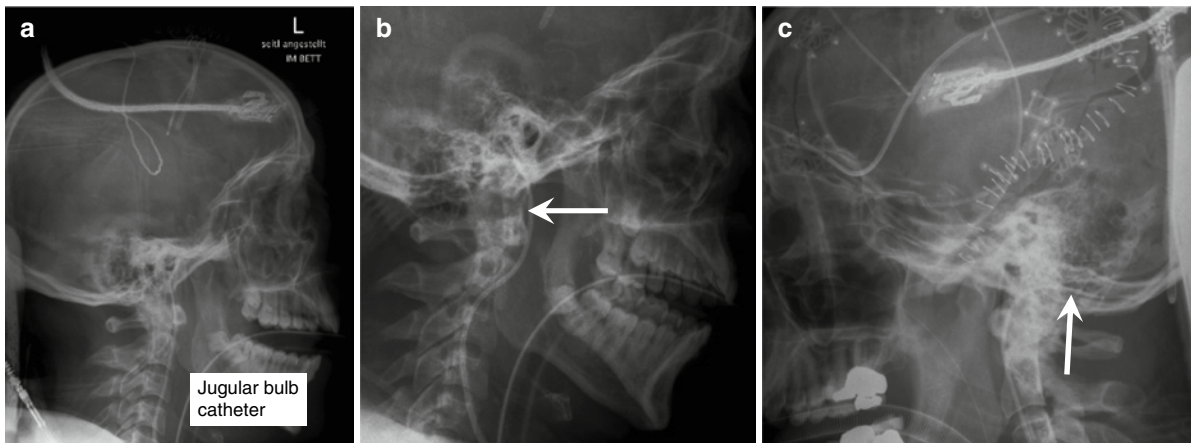


Fig. 2.8 Example of correct placement of a jugular bulb catheter verified in a lateral conventional X-ray of the cervical spine/head (a). The tip of the catheter inserted in the larger internal jugular vein should be clearly visible at the height of the mastoid process to approximately 1 cm below the mastoid process. Excessively inserted catheters (b and c) increased the risk of

sinus vein thrombosis. Insufficient depth with the tip of the catheter remaining at the height of the mandible (inflow of the facial vein to the internal jugular vein) will falsely influence jugular venous oxygen saturation ($SjvO_2$) values, resulting in elevated values due to lower oxygen consumption of the facial muscles

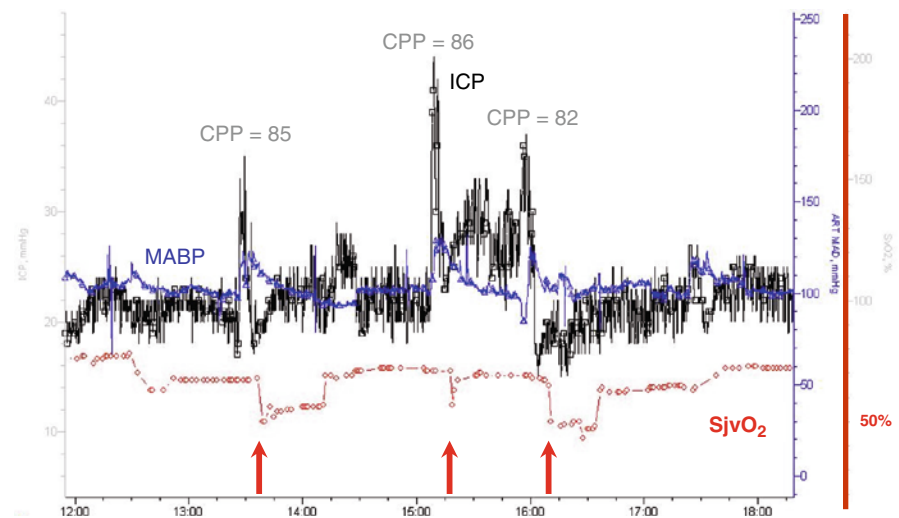
the catheter is butting against the skull base and must be retracted by 1–2 cm (Fig. 2.8b). A follow-up X-ray should be performed to document the correct placement following correction of the insertion depth. Cannulation of the sinus vein resulting from deep penetration of the internal jugular vein can be unmasked by conventional X-ray (Fig. 2.8c).

Continuous recording of the $SjvO_2$ allows unmasking the pathologic impact of elevated ICP even in case of “adequate” CPP (Fig. 2.9). However, the employed light cables exhibit a loss in quality within the first 24 h and the diameter of the catheters (especially

pediatric pulmonary artery catheters) increases the risk of thrombus formation within the internal jugular vein. The risk of thrombus formation can be minimized by using a single-lumen central venous catheter. This alternative, however, only allows discontinuous investigations based on intermittent arterial and jugular venous blood gas analysis (BGA).

Use of the jugular venous catheters allows to analyze $SjvO_2$, calculate various metabolic indices (e.g., oxygen-glucose index (OGI), lactate-oxygen index (LOI), lactate-glucose index (LGI)) [29], determine the oxygen extraction ratio (OER), and calculate differences

Fig. 2.9 Illustrative example reflecting the necessity of integrating multimodal monitoring in routine intensive care in patients with severe traumatic brain injury (TBI). Intermittent increases in intracranial pressure (ICP) due to disturbed cerebral autoregulation (A-waves) resulted in reduced cerebral perfusion and impaired cerebral oxygen supply despite adequate cerebral perfusion pressure (CPP) (80–90 mmHg). This was only unmasked by concomitant analysis of changes in jugular venous oxygen saturation <50%



(arterio-jugular venous lactate difference) which together facilitate in-depth assessment of posttraumatic energetic disturbances [30]. Contrary to the microdialysis technique this easy-to-use and inexpensive tool does not require an adaptation period and can be performed on any intensive care unit (ICU) without expensive and difficult analysis and time-consuming upkeep, which also requires substantial experience. However, microdialysis cannot be substituted by the jugular venous blood analyses. This simple technique is excellent to unmask pathologic metabolic alterations within the first hours following severe TBI even under conditions of normal ICP <15 mmHg. In addition, it allows to bridge the time until insertion of microdialysis and ptiO_2 . Thus, we can attain a semi-continuous monitoring and have the possibility of adapting our therapeutic interventions based on objective parameters and monitoring results. In approximately 70% of our patients we observe signs of early metabolic impairment due to inadequate depth of sedation which is missed when only focusing on ICP values.

The theoretic advantage of continuously assessed SjvO_2 using fiber-optic transmission compared to the discontinuous, i.e., intermittent, BGA is limited by the increase in artifacts over time and the higher risk of thrombus formation due to the larger catheters.

The SjvO_2 reflects changes in cerebral oxygen supply, cerebral perfusion, and cerebral oxygen consumption as SjvO_2 correlates directly with perfusion and correlates inversely with cerebral oxygen consumption. Thus, an increase in MABP with a subsequent amelioration of the CPP as well as reduced hyperventilation to controlled hypoventilation will improve cerebral oxygen supply due to increased perfusion. Reducing cerebral

oxygen consumption due to pharmacologic inhibition of neuronal activity by increasing the dose of benzodiazepines, barbiturates, or propofol or by reducing brain temperature will also increase SjvO_2 due to metabolic stabilization.

It is important to acknowledge that jugular venous values reflect global changes within the brain which correlate well with local measurements (ptiO_2) [31]. In some patients we observe discrepancies between elevated ptiO_2 and decreased SjvO_2 values following prolonged analgesia and sedation, which suggests regionally heterogeneous functional alterations within the white matter/cortex transition (ptiO_2) and basal ganglia (SjvO_2). This could result from functional adaptations due to prolonged sedation-induced glutamate receptor downregulation and compensatory increase in adrenergic, dopaminergic, and cholinergic excitation.

Based on the validation studies comparing SjvO_2 with ptiO_2 , Kiening and colleagues [31] demonstrated that $\text{SjvO}_2 \leq 50\%$ reflects cerebral ischemia and should be avoided and corrected immediately [32] since this is associated with metabolic perturbation [33] and an increased mortality and morbidity [34] (Table 2.5). In this context, elevated CPP, reduced hyperventilation, induced hypoventilation, decreased temperature, and increased depth of sedation can be used to correct signs of impaired cerebral perfusion. In case of low hemoglobin levels transfusion of red blood cells should be considered. The data concerning changes in arterio-jugular venous lactate differences is less clear and convincing [35, 36]. This could stem from the fact that the brain is capable of consuming lactate and ketone bodies as alternative energetic compounds under

Table 2.5 Jugular venous oxygen saturation (SjvO_2), threshold values, and possible therapeutic interventions

SjvO_2 values	Meaning	Reasons	Therapy/implications
<55%	Ischemia With increased jugular venous lactate: severe ischemia → fast correction required	Hyperventilation Inadequate analgesia/sedation Insufficient CPP Vasospasmus (TCD) Vasospasm Fever anemia	Normo-/hypoventilation Increase analgesia/sedation Elevate CPP Increase CPP Reduce temperature Transfuse red blood cells
55–75%	Normal values		
>75%	Hyperemia (TCD) = luxury perfusion	Vasodilatation Disturbed autoregulation Elevated CPP Deep analgesia/sedation severe brain damage (>80%)	Hyperventilation Reduce CPP Decrease analgesia/sedation Search for signs of extensive brain damage

pathologic conditions [37]. From an energetic point of view this, however, is less effective than the entire glycolytic pathway including oxidative phosphorylation, which requires intact enzymes and functionally active mitochondria. For the alternative lactate metabolism the glial–neuronal lactate shuttle plays an important role as lactate produced in astrocytes is transported to neurons for subsequent consumption. The glial lactate stems from glutamate which was previously released by neurons and then metabolized to lactate within the astrocytes due to sustained glycolysis [38].

In this context, it is important to acknowledge that cerebral oxygen consumption and thus $SjvO_2$ (as well as $ptiO_2$) and the arterio-jugular venous lactate difference are strongly influenced by brain temperature, depth of sedation, and cerebral perfusion. For example, $SjvO_2$ values $>90\%$ are observed in cases of barbiturate-induced suppression of electroencephalogram (EEG) activity (isoelectric line).

$SjvO_2$ values $>80\%$ can reflect underlying hyperemia as assessed by TCD, provided the patients' anatomy allows TCD analysis. Such hyperemia or luxury perfusion allows to reduce CPP and to use controlled hyperventilation to decrease pressure, increasing expansion of the intracranial blood volume. Whenever TCD is not available to document hyperemia, $SjvO_2 > 80\%$ and $ptiO_2 > 30$ mmHg in face of an adequate depth of sedation (e.g., BIS < 40) can be used to unmask hyperemia. In parallel increased $SjvO_2$ values $>90\%$ and $ptiO_2$ values >40 mmHg can also reflect extensive brain damage resulting in loss of oxygen consumption due to extensive cell damage and cell loss. To differentiate hyperemia, deep pharmacologic coma, and extensive irreversible brain damage all available monitoring parameters (ICP, temperature, bispectral index EEG (BIS EEG), EEG, somatosensory evoked potential (SEP), $ptiO_2$), including imaging (CT with angiography), must be considered (Table 2.5).

Calculation of different indices, e.g., LOI, LGI, and OGI, has not yet been introduced in daily intensive care routine [30]. These indices allow to determine the different reasons of metabolic perturbation. In this context, the OGI ($OGI = avDO_2/AJVD$ glc) at values <6 reflects anaerobic glycolysis while $OGI > 6$ characterizes cerebral lactate consumption; the LGI ($LGI = AJVD \text{ lac}/AJVD \text{ glc}$) can be used to differ lactate production (negative values) from lactate uptake (positive values). The LOI ($LOI = AJVD \text{ lac}/avDO_2$) allows to characterize the relationship between anaerobic and oxidative metabolism: while negative LOI values reflect cerebral lactate production positive

values unmask cerebral lactate uptake. The calculated OER ($OER = (caO_2 - cjvO_2)/caO_2$) allows insight into cerebral oxygen consumption.

The analysis of transcerebral gradients of humoral and cellular constituents is still subject to more in-depth analysis and has not yet been integrated in clinical diagnostics and intensive care-related decision making [39].

2.4.2.1 Crucial Points and Pearls

- Insertion of a jugular venous catheter allows in-depth insight into otherwise occult intracerebral pathophysiologic processes.
- Ultrasonographic guidance allows identification of the dominant, i.e., larger, internal jugular vein and minimizes the risk of accidentally puncturing the carotid artery.
- $SjvO_2$ differentiates insufficient oxygen supply due to impaired cerebral perfusion ($SjvO_2 < 50\%$) from reduced cerebral oxygen consumption encountered during hyperemia ($SjvO_2 > 80\%$), thus allowing to initiate and control different specific therapeutic interventions.
- Unmasking metabolic alterations is the prerequisite to guide the extent and duration of therapeutic interventions such as hyperventilation, CPP level, transfusion of red blood cells, oxygenation, with the aim of avoiding secondary brain damage.

2.4.3 Microdialysis

Cerebral microdialysis with a diameter of 0.3 mm allows detailed insight in otherwise hidden metabolic alterations (Fig. 2.10). Depending on the used size of the pore size of the semipermeable membrane at the tip of the catheter substances with small to large molecular weights can be filtered from the extracellular space according to their existing concentration gradients. In clinical routine, bedside analysis allows enzymatic analysis of glucose, lactate, pyruvate, glycerol, and glutamate (www.microdialysis.se). Calculating various ratios, e.g., lactate/pyruvate, lactate/glucose, lactate/glutamate, allows a more detailed characterization of the underlying metabolic perturbation even at normal ICP levels and at normal concentrations of the different parameters [40]. Furthermore, various proteins can be determined [41] which have not yet been integrated in contemporary clinical decision making.

Fig. 2.10 Overview of the different probes used in specialized centers in intensive care routine: intracranial pressure (ICP), partial pressure tissue oxygenation (ptiO₂), temperature, microdialysis. These different probes are much smaller than the diameter of a conventional paper clip, with the ICP probe having the largest diameter

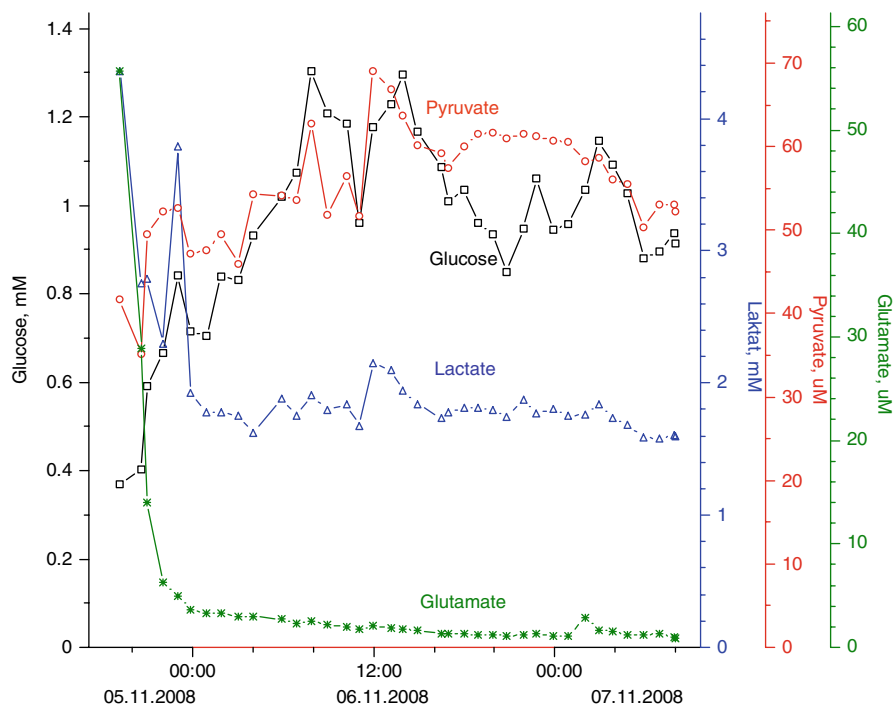
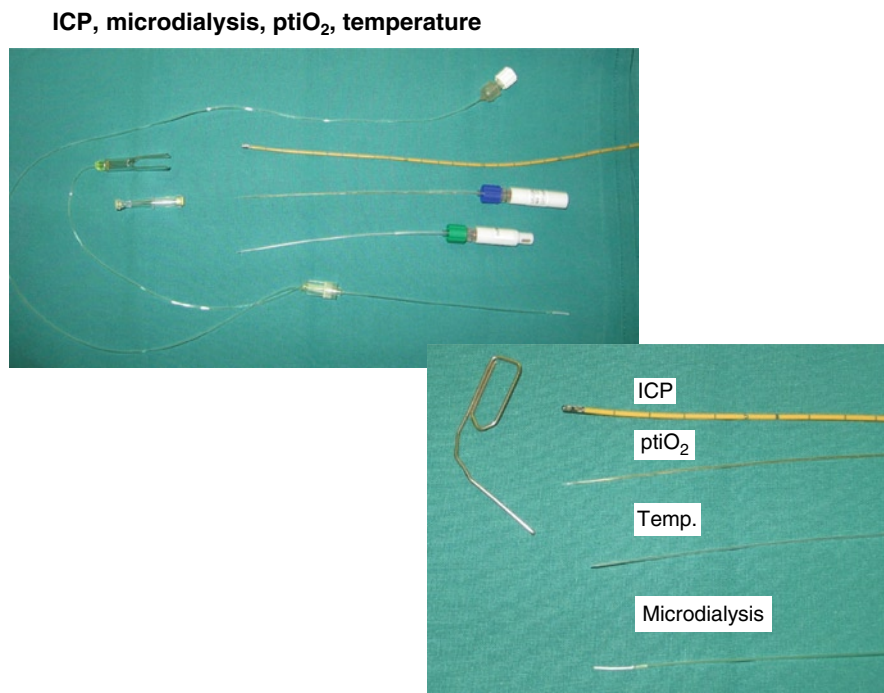


Fig. 2.11 Insertion of the microdialysis catheter induces a local injury reflected by increased extracellular glutamate and lactate levels followed by a steady decrease during the subsequent 2–4 h reaching stable values

Insertion of the microdialysis catheter induces a local tissue trauma which is predominantly reflected by significantly increased glutamate concentrations. Thus, the initial values cannot be used for clinical decision making. By experience

metabolic parameters reach stable values within the first 4 h (Fig. 2.11). As a consequence microdialysis cannot be used for clinical decision making during the first hours after TBI, a phase which is characterized by hypotension and hyperventilation during

the initial treatment in the emergency and operating rooms.

With microdialysis, both dialysis velocity and investigated time interval are important variables which influence concentration of the different parameters and determine the investigated time frame. In clinical routine, dialysis velocities between 0.3 and 1 $\mu\text{L}/\text{min}$ combined with an interval of 60 min are commonly used. This means that clinical decisions are based on metabolic changes which have already occurred in the previously investigated time span. Consequently, the metabolic alterations unmasked by microdialysis should always be judged together with other parameters.

A technical limitation is the *in vivo* recovery rate which depends on changes within the tissue (hemorrhage, glial scar formation), the used dialysis velocity, and the type of membrane used. In this context, recovery rate correlates inversely to the dialysis velocity [42], which results in lower absolute concentrations of the different parameters at higher velocities and higher concentrations at lower velocities. Consequently, concentrations of the metabolic parameters determined at a dialysis velocity > 0.3 $\mu\text{L}/\text{min}$ must be multiplied by

a correction factor, especially if results described in different publications are to be compared and if reference values are to be defined for the clinical routine (Fig. 2.12).

Microdialysis catheters can either be inserted under visual control during neurosurgery (e.g., craniotomy or craniectomy) or be introduced via a burrhole during initial neurosurgery or later on the ICU. For this, a commercially available specialized guiding/bolt system (www.integra-ls.com) is used through which different probes, e.g., microdialysis, ptiO_2 , temperature probe, and ICP, can be inserted. (Officially, insertion of microdialysis probes is an off-label procedure.) Thus, local changes can be determined at a predefined penetration depth. Reproducibility of the insertion depth and area of interest is strongly influenced by the angle at which the burrhole is drilled (Fig. 2.13). Insertion of microdialysis during neurosurgery also allows strict cortical positioning compared to the white matter/grey matter junction when using the bolt system. Overall, it is of utmost importance not to insert the different probes in the pre- and postcentral gyrus to avoid serious damage resulting in a sensory or motoric hemisindrome. The exact area of insertion in relation to the

Fig. 2.12 Changing flow velocity from 1 to 0.1 $\mu\text{L}/\text{min}$ and back to 1 $\mu\text{L}/\text{min}$ significantly increases concentrations of the dialyzed metabolites. This clearly demonstrates the impact of flow velocity on the *in vivo* recovery rate. This must be considered when comparing data derived in different studies using different flow velocities

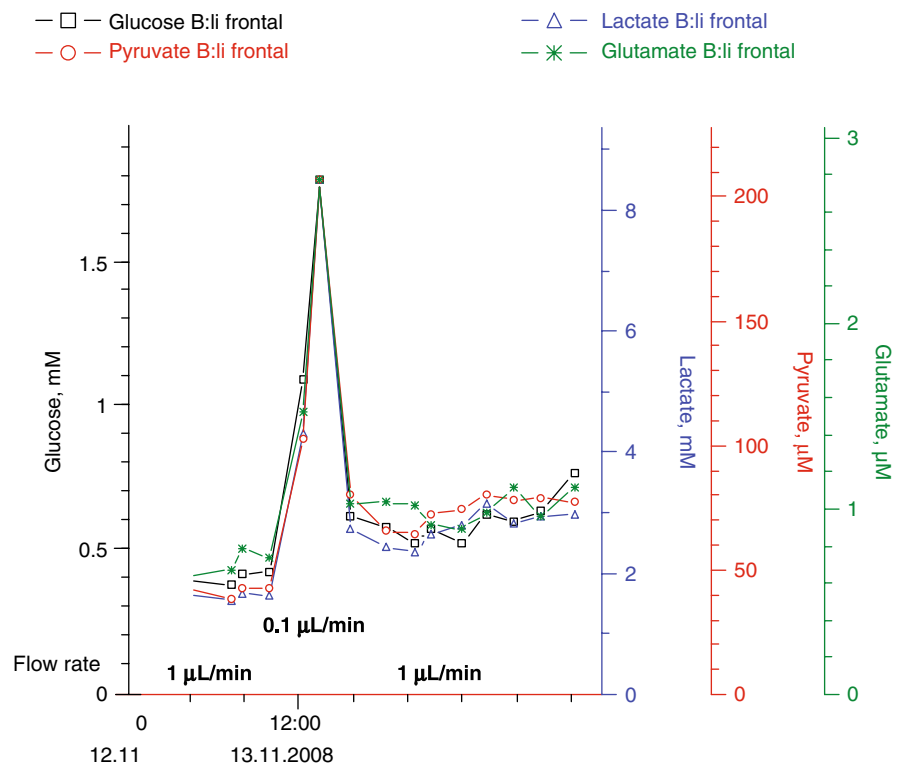
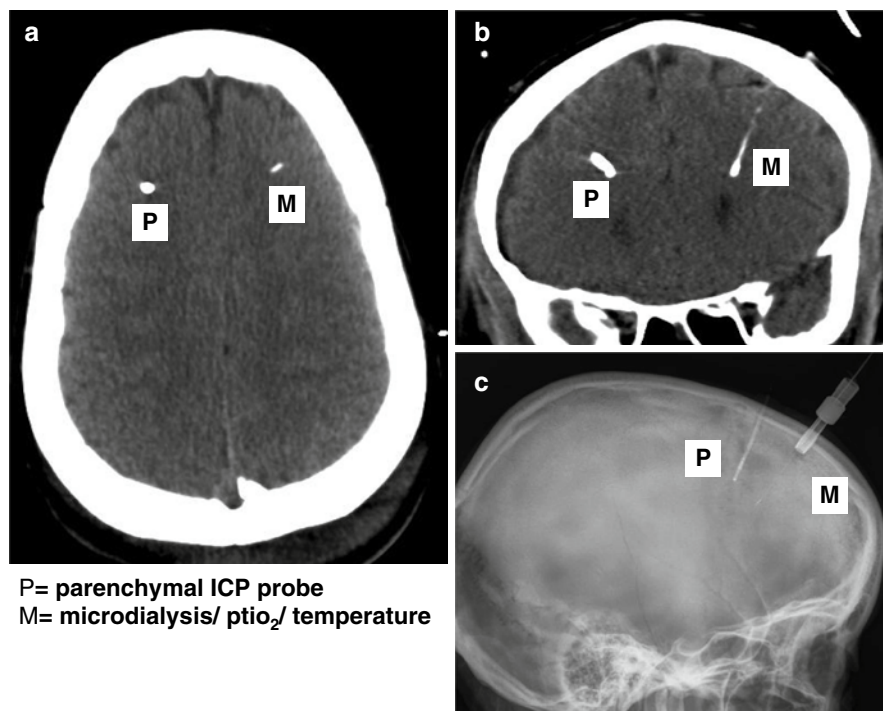


Fig. 2.13 Examples of insertion of parenchymal intracranial pressure (ICP) probe (*P*) and microdialysis combined with partial pressure tissue oxygenation (ptiO₂) and temperature probe (*M*) (using the same burrhole). Figure 2.13a and b depict projection of probes in axial (a) and coronal (b) computed tomography (CT) scans. Projection of the inserted probes is also seen in the lateral aspect of a conventional X-ray of the head (c)



present lesions and the number of catheters which should be used is still discussed controversially.

Similar to the regional heterogeneity of interhemispheric pressure gradients and between the supra- and infratentorial compartments metabolic alterations also show regional differences [43]. Nonetheless, an increase in ICP as well as local and global pathologic influences (e.g., hypotension, hyperemia, vasospasm, hyperventilation, fever, epileptic discharges) induces metabolic alterations. In addition, positive therapeutic effects result in an improvement of signs of metabolic deterioration [44] and integration of microdialysis allows to reduce CPP in a controlled manner to as low as 50 mmHg [45] as practiced within the “Lund-concept.” Apart from the absolute values and the relative changes of the different metabolic parameters over time the lactate/pyruvate ratio is routinely used to determine the severity of underlying metabolic impairment. In this context, an increased lactate/pyruvate ratio exceeding 30 which coincides with low cerebral extracellular glucose levels <0.3 mmol/L reflects massive energetic derangement even in face of adequate oxygenation determined by ptiO₂ (Fig. 2.14). This pattern is understood as a sign of severe functional mitochondrial disturbance: glucose is excessively metabolized nonoxidatively, which explains the low extracellular glucose levels; concomitantly lactate is produced while pyruvate cannot be regenerated due to

missing oxidative phosphorylation resulting from disturbed mitochondrial respiratory chain accounting for the increased lactate/pyruvate ratio. In addition, other pathophysiologic alterations such as vasospasm, epileptic discharges, and CSD must be actively searched. A pathologic increased lactate/pyruvate ratio is associated with subsequent chronic frontal lobe atrophy and thus deserves intensified consideration [46]. Whether this can be prevented by our present therapeutic interventions warrants further investigation. Combinational investigations using microdialysis and sophisticated imaging such as positron emission tomography (PET) shows that glucose can be metabolized to lactate as well as pyruvate without increasing the lactate/pyruvate ratio [47], suggesting that other pathologic processes must be considered.

Elevated extracellular glutamate levels reflect strong/excessive neuronal excitation or signs of severe cell damage resulting in extrusion of intracellularly stored glutamate in millimolar concentrations compared to micromolar concentrations within the extracellular space. Increased lactate levels exhibit an energetic deficit while decreasing glucose levels can result from increased cellular uptake and metabolism and/or insufficient supply due to systemic hypoglycemia or insufficient expression of glucose transporters. Elevated glycerol values reflect membrane damage.

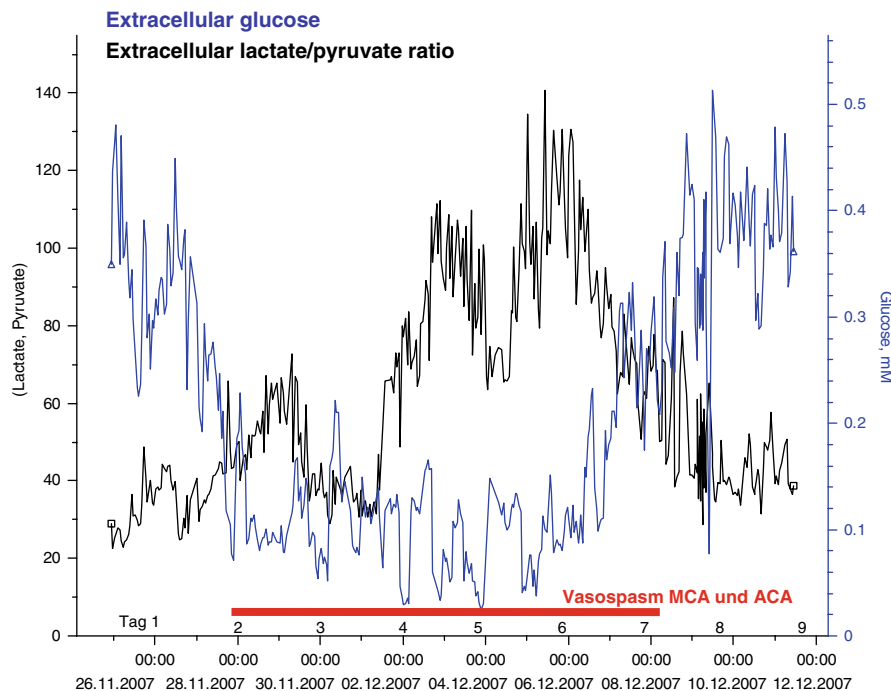


Fig. 2.14 Using cerebral microdialysis allows to differentially search for metabolic disturbances which can be harbingers of additional pathologic alterations. This illustrative case shows an increase in lactate/pyruvate ratio with concomitant decrease in extracellular glucose on the second posttraumatic day in the face of initially normal lactate/pyruvate ratio and normal extracellular glucose levels (CMA 70, flow rate: 1 μ L/min, interval: 60 min). Between days 4 and 6 lactate/pyruvate ratio increased

further and extracellular brain glucose decreased below 0.2 mM. Thereafter, pathologic values normalized. In this patient, this pathologic metabolic pattern was induced by severe vasospasm in the ipsilateral middle cerebral artery (MCA) and anterior cerebral artery (ACA). In a different patient this pattern coincided with epileptic discharges. Resolution of vasospasm and disappearance of epileptic discharges coincided with resolving pathologic metabolic alterations

Overall, microdialysis can be used to unmask pathologic changes, characterize pathologic relevance of certain alterations, and guide therapeutic interventions (e.g., hyperventilation, oxygenation, sedation, CPP level).

As recently shown by Belli and colleagues the early use of microdialysis corresponds to an early warning system since metabolic alterations unmask pathologic alterations and precede increases in ICP [22].

2.4.3.1 Crucial Points and Pearls

- Microdialysis allows detailed insight into metabolic alterations which otherwise remain hidden in the difficult-to-access brain.
- Local changes can be used to guide therapeutic interventions.

- Due to its time-consuming maintenance and additional costs microdialysis cannot be implemented in all centers yet.

2.4.4 Tissue Oxygenation- $ptiO_2$

Insertion of $ptiO_2$ probes is performed similar to the technique of implanting a microdialysis catheter [48], which can be performed during neurosurgery or on the ICU via a frontal burrhole and a specialized bolt system (Fig. 2.15). Location of the $ptiO_2$ probe in relation to cerebral lesions and the number of probes are discussed controversially. To minimize the risk for additional injuries, i.e., hemorrhage in edematous frontal lobe, the different probes ($ptiO_2$, microdialysis, temperature, with/without ICP) are usually positioned in the lesser injured hemisphere. The choice of the side of insertion

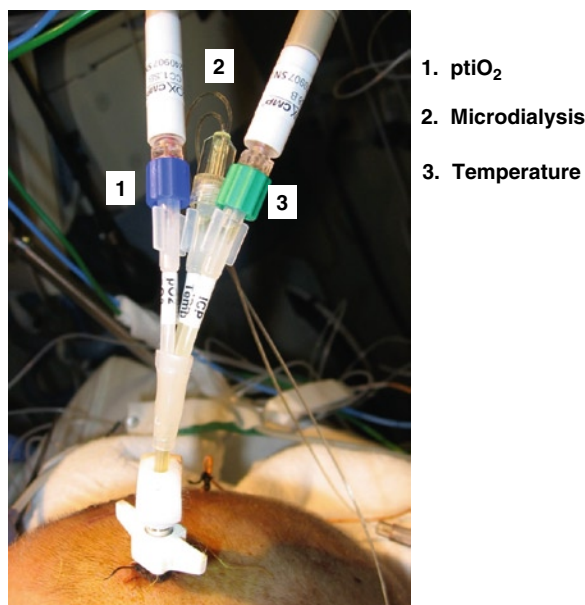


Fig. 2.15 Picture showing usage of a commercially available bolt system via which a partial pressure tissue oxygenation (ptiO₂) probe (1), a microdialysis catheter (off-label use) (2), and a temperature probe (3) are inserted in the frontal lobe

depends on the predefined interest, i.e., if evolving pathologic alterations are to be unmasked in the more severely injured hemisphere or if new signs of tissue damage are to be diagnosed in the lesser or uninjured hemisphere. In this context it is important to remember that the CT scan does not reveal signs of functional and metabolic damage and that missing structural lesions do not guarantee normal metabolism and function.

The commonly used highly flexible ptiO₂ probe is a so-called Clark-type sensor (www.integra-ls.com) with a diameter of 0.55 mm and with which ptiO₂ is determined polarographically: within the sensor membrane oxygen is reduced at the cathode, thereby changing the polarizing current between anode and cathode. Changes within the electric circuit are proportional to the partial oxygen pressure within the tissue. The measured ptiO₂ depends on the tissue temperature and thus requires correction, which is automatically performed if a specialized temperature sensor is used. Novel probes such as Neurovent PTO® allow simultaneous analysis of ICP, ptiO₂ and temperature, which are combined within one probe (www.raumedic.de).

As determined in validation studies ptiO₂ values <10 mmHg (Licox®) reflect tissue hypoxia which is associated with an increase in extracellular glutamate if not corrected within 30 min [49, 50] and correlates clinically with neuropsychologic deficits in survivors [51].

Although ptiO₂ show local changes these values correlate very well with pathologic S_{ijv}O₂ values [31], which reflect global cerebral alterations and thus allow to guide type and extent of therapeutic interventions.

Similar to S_{ijv}O₂ ptiO₂ values indirectly reflect cerebral perfusion [52]. In this context, low S_{ijv}O₂ and ptiO₂ values unmask reduced cerebral perfusion due to, for example, systemic hypotension or local cerebral vasoconstriction caused by hyperventilation or vasospasm. In parallel, signs of increased oxygen consumption due to increased neuronal activity (insufficient analgesia/sedation, epileptic discharges, systemic hypoglycemia) as well as insufficient oxygen supply (anemia, impaired cardiac output, insufficient oxygenation) must be searched and corrected. Thus, determining S_{ijv}O₂ and ptiO₂ allows to perform detailed and controlled therapeutic corrections. In this context, we can decide whether ventilation, hemodynamic support, hematocrit, or blood glucose must be corrected (Table 2.6).

Abnormally elevated ptiO₂ and S_{ijv}O₂ values >30 mmHg and ≥80%, respectively, strongly suggest reduced cerebral oxygen consumption most likely due to excessively deep sedation and metabolic uncoupling of cerebral perfusion. This metabolic uncoupling is associated with strong vasodilation, which results in hyperemia and global luxury perfusion. In conjunction with a disturbed autoregulation due to impaired vasoconstriction hyperemia elevates ICP due to an increase in intracranial blood volume [53].

Apart from guiding paco₂ levels in terms of controlling hyperventilation ptiO₂ values can also be used to individually define adequate CPP and oxygenation limits and targets [54], and also determine the necessity of transfusing red blood cells during otherwise stable intensive care conditions [55]. In this context, transfusion of oxygen carriers in patients with a hematocrit < 30% will only induce a persisting increase in ptiO₂ > 15 mmHg if the ptiO₂ is below 15 mmHg. Thus, patients with a baseline ptiO₂ > 15 mmHg do not profit from red blood cell transfusions. This, in turn, allows to reduce the number of unnecessary red blood cell transfusions.

2.4.4.1 Crucial Points and Pearls

- Measuring tissue oxygenation, i.e., ptiO₂, allows to unmask reduced perfusion and insufficient oxygen supply (<10 mmHg) and also unmasks underlying hyperemia (>30 mmHg).

Table 2.6 Threshold values of partial pressure tissue oxygenation (ptiO₂), their meaning and possible therapeutic options

ptiO ₂ values	Meaning	Reason	Treatment
<10 mmHg	Ischemia With elevated glutamate, lactate, glycerol, L/P ratio: severe ischemia → immediate correction required	Hyperventilation Inadequate analgesia/sedation Insufficient CPP Impaired cardiac output Vasospasm (TCD) Fever Anemia Hypoxia	Normo- to hypoventilation Increase analgesia/sedation Elevate CPP Administer volume, inotropics Increase CPP Reduce temperature Transfusion of red blood cells Improve oxygenation
>15 mmHg	Normal values		
>30 mmHg	Hyperemia (TCD) = luxury perfusion	Vasodilatation Disturbed autoregulation CPP too high Cardiac output too high Sedation too deep Oxygenation too severe	Hyperventilation Reduce CPP Decrease CPP Reduce volume and inotropics, search for SIRS, sepsis Reduce sedation Decrease paO ₂ , allow lower hematocrit

- ptiO₂ values facilitate controlled adaptation of therapeutic interventions and thus allow to prevent potentially harmful consequences of insufficient or excessive interventions.
- Useful decisions, however, can only be made if these values are considered in conjunction with other metabolic variables and systemic changes.
- Metabolic alterations determined by microdialysis allow to define the individual pathologic ptiO₂ threshold.

2.4.5 Analysis of Cerebrospinal Fluid

In patients with a noncollapsed and noncompressed ventricular system an EVD can be inserted which allows therapeutic drainage of CSF with the aim of reducing elevated ICP. In addition, CSF can be used for diagnostic purposes by analyzing different mediators and markers of tissue damage and regeneration processes [56–63]. Moreover, pharmacodynamic as well as pharmacokinetic properties can be characterized [64–67]. Possible methodological difficulties lie within the nature of the EVD itself which need to be considered when interpreting the obtained results. In this context, CSF levels of different parameters are influenced by the presence of intraventricular blood, diffusion of edema from the parenchyma to the ventricular system, and production and absorption of CSF by the choroid plexus. These different influences are usually not

considered in clinical routine. The distance of lesions to the ventricular system is also important [68].

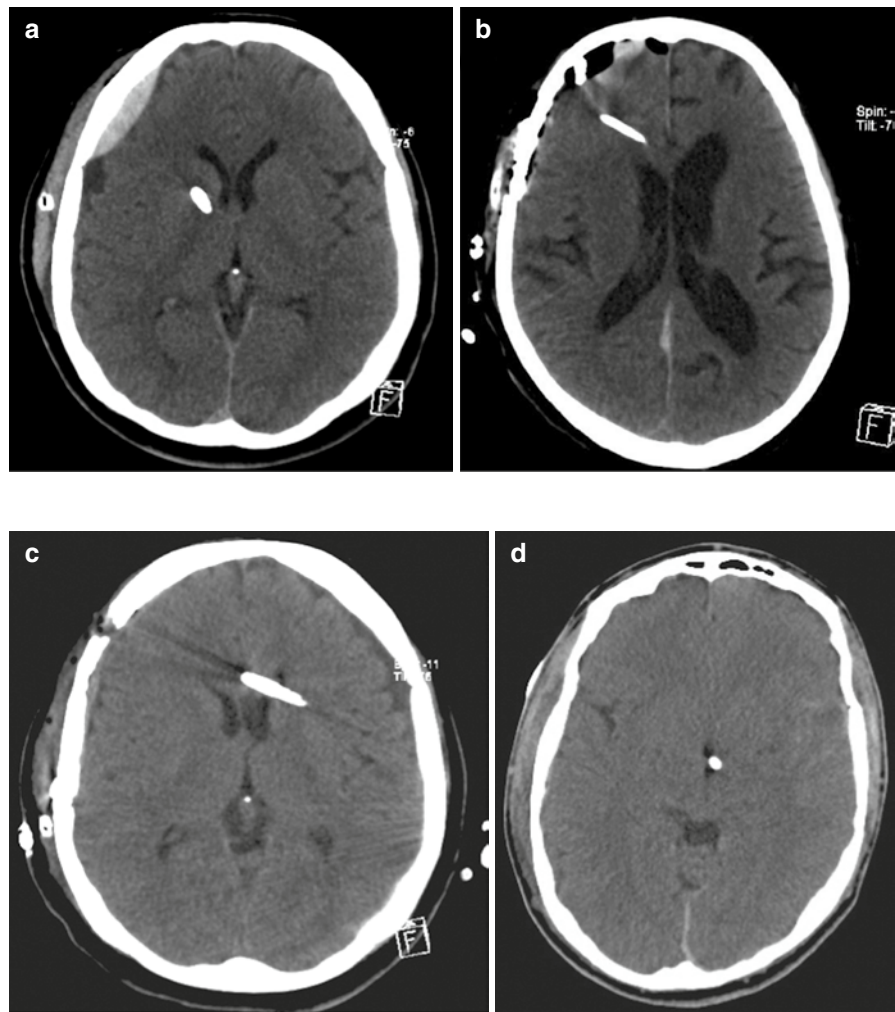
In addition, there is no clear consensus whether one daily measurement is sufficient or whether repetitive or even continuous analysis must be performed. Since EVDs cannot be placed in all patients and since CSF drainage can subside due to evolving edema formation a heterogeneous population of patient is assessed: those with a “less severe” primary injury and those who show tremendous secondary progression of brain edema. Patients with very severe primary damage are “excluded.” Thus, general applicability of the obtained data is limited.

Different complications such as iatrogenic injury to basal ganglia or the internal capsule (Fig. 2.16) as well as the increased risk of ventriculitis and meningitis decrease its wide application [69].

2.4.5.1 Crucial Points and Pearls

- Analysis of CSF allows to determine pathophysiologic changes and characterize pharmacologic profiles.
- Since CSF analysis requires introduction of an EVD not all patients can be investigated. Relevant data can only be obtained if the ventricular system is wide enough and if it is not compressed by evolving brain edema.
- To date, therapeutic decisions cannot be based on changes determined in CSF.

Fig. 2.16 Examples showing injuries induced by inserting external ventricular drainage (EVD): internal capsule (a), corpus callosum (b), corpus callosum and contralateral caudate nucleus (c), and thalamus (d)



2.4.6 Electrophysiologic Studies: Electroencephalogram, Sensory Evoked Potential, Cortical Spreading Depression

2.4.6.1 EEG and SEP

Functional changes in neuronal activity and axonal information transmission can be assessed by electrophysiologic investigations, e.g., EEG, SEP, or acoustic evoked potential (AEP). These investigations also have a certain prognostic value in severe TBI. This is the case whenever an isoelectric EEG results from severe global brain damage as seen in hypoxia and excluded

pharmacologic or toxicologic etiology, and whenever evoked potentials lack appropriate brain stem and cortical responses with missing amplitudes and long latencies at specific anatomic points.

EEG analysis reflects summation potentials generated by excitatory and inhibitory processes within cortical and subcortical areas which are subject to modulatory influences originating within the brain stem and basal ganglia. These processes result in specific frequencies and amplitudes. Simply phrased frequencies and amplitudes correlate inversely: low-frequency bands (delta: δ , tau: τ) exhibit large amplitudes (slow waves) while high-frequency bands (alpha: α , beta: β) show low amplitudes (fast waves). Slow waves/low frequency bands are found in sleep and during pharmacologic

coma while fast waves/high frequency bands reflect arousal activity.

Evoked potentials are used to assess intact axonal impulse transmission and adequate central processing within the cortex by analyzing transmission time (latency) and strength of cortical processing (amplitude) at standardized and predefined points in response to exteroceptive tactile, acoustic, and nociceptive stimuli.

EEG and evoked potentials require specialized and well-trained personnel to perform these investigations and to accurately interpret the obtained curves. While the EEG can be recorded continuously, evoked potentials can only be performed discontinuously on the ICU. This, in turn, does not allow to dynamically unmask progressive brain stem pathology in real time.

Changes within the different EEG frequency spectra and amplitudes are also influenced by the lesions themselves, concomitant analgesia/sedation, hypothermia, and hyperventilation.

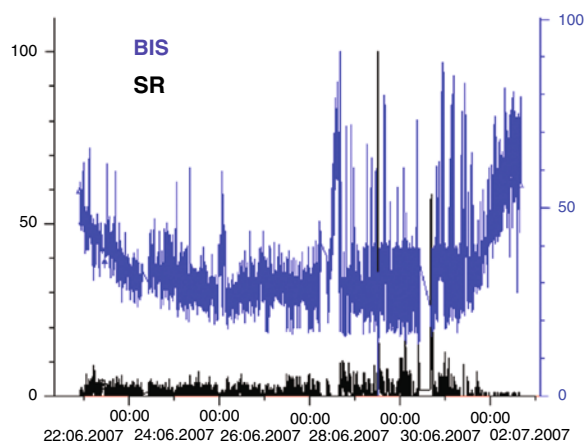
Pathologic changes in evoked potentials have a very good prognostic potency regarding mortality and morbidity [70]. However, this is not the case for

EEG analysis, which is due to the underlying pharmacologic interference that results in an increase in δ and τ frequency bands. A further difficulty is to interpret shifts within the frequency bands which are not determined in all hospitals. In this context, posttraumatically reduced variability of the alpha frequency gains increasing prognostic importance as this is associated with significantly reduced regeneration [71, 72].

Interpretation of isoelectric line can be very difficult as it could result from the continuous administration of barbiturates and propofol or could reflect brain death. Neurologic examination and imaging including angiography to exclude compression of large intracerebral arteries might be required to differentiate cause and nature of an isoelectric line.

By the use of modern and simplified EEG methods (BIS EEG® – www.aspectmedical.com/Narcotrend® – www.narcotrend.de) changes in neuronal activity – even between the two hemispheres – can be assessed in clinical routine at the bedside without extensive training. These EEG techniques are usually used to guide sedation and barbiturate coma (Fig. 2.17).

a Analgesia, sedation: fentanyl and midazolam



b Influence of thiopental

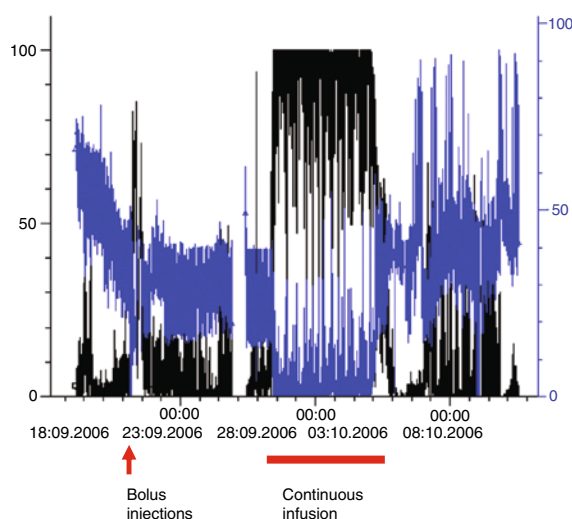


Fig. 2.17 Examples showing changes in neuronal activity determined by bispectral index electroencephalogram (BIS EEG®) (blue curve = BIS, black curve = suppression rate) in a patient subjected to analgesia and sedation following severe traumatic brain injury (TBI) (a) and a patient requiring continuous thiopental infusion due to increase in intracranial pressure (ICP) > 25 mmHg (b). (a) During continuous infusion of fentanyl and midazolam and corresponding increase in drug doses BIS value reflecting depth of analgesia/sedation was reduced

and maintained between 20 and 40, our target. During controlled dose reduction of fentanyl and midazolam (10% per day) and concomitant infusion of propofol and clonidine to treat vegetative and motoric signs of withdrawal from fentanyl and midazolam BIS slowly increased >60 and the patient awoke slowly. (b) Additional thiopental infusion (0.5–3 mg/kg/h) reduced BIS value below 20 and coincided with a corresponding increase in suppression rate >60%, reflecting increased depth of pharmacologic coma

2.4.6.2 CSD (cortical spreading depression)

The phenomenon of CSD initially described in 1944 by Leão [73] results from neuronal and glial depolarization which traverses the cortex in a wave pattern and is associated with energy-consuming processes. These pathologic alterations contribute to the secondary growth of a preexisting lesion which is also observed under clinical conditions [74, 75]. Initiating factors are elevated extracellular potassium concentrations, decreased cerebral NO levels, and reduced blood glucose concentrations [76]. In addition, low cerebral glucose levels appear to induce CSD, which is associated with increased extracellular lactate [77]. To determine these functional disturbances a special sensor with several electrodes must be positioned on the cortical surface under the dura. This requires a neurosurgical intervention and can only be performed by specialized neurosurgeons. With these sensors temporal and regional changes in electric activity occurring between the individual electrodes are visualized.

Ongoing research conducted in different European centers focuses on the pathophysiologic characterization and identification of possible therapeutic interventions (www.cosbid.org).

2.4.6.3 Crucial Points and Pearls

- Electrophysiologic investigations (EEG, SEP) are helpful in assessing functional alterations and also have certain prognostic value.
- Results obtained by EEG and SEP must always be interpreted in the context of the clinical situation and structural lesions unmasked with conventional imaging (CT, magnetic resonance imaging (MRI)) before definite decisions may be drawn.
- Simplified EEG analyses (BIS EEG®, Narcotrend®) are used in the clinical routine to continuously assess and control sedation by the ICU staff.
- Insertion of specialized sensors to assess CSD known to induce evolving tissue damage is currently only performed in specialized centers.

2.4.7 Assessment of Cerebral Perfusion

Since the initial description of extensive cerebral infarctions by Graham and colleagues in the year 1978

in patients who succumbed to their severe TBI, cerebral perfusion deficit has reached strong pathophysiologic importance [78]. Identification of insufficient cerebral perfusion as well as correction of this perfusion deficit is of imminent importance in modern intensive care treatment following severe TBI. While impaired perfusion with ensuing ischemia due to microthrombosis formation and vasospasm is predominantly found early after TBI (hours to days), sustained perfusion, i.e., hyperemia, is encountered days to weeks after TBI. The easiest way to guide cerebral perfusion is to calculate CPP by subtracting ICP from MABP. However, this is only a crude estimation of global cerebral perfusion and does not guarantee adequate cerebral perfusion in all brain regions which requires more sophisticated direct or indirect, invasive or noninvasive methods. For this, special probes such as thermodilution or Laser Doppler probes can be used [79]. While these techniques only show local alterations the transcranial thermodilution method, Xenon-enhanced CT, perfusion CT, single photon emission computed tomography (SPECT), PET, and perfusion-weighted MRI can be used to visualize both local and global changes in cerebral perfusion [79, 80]. Applicability in the daily intensive care routine of these imaging techniques is limited due to logistic, technical, and time-consuming restraints and the fact that the imaging only reflects a snapshot picture of actual alterations at the time point of analysis. Thus, these images can only partially aid in adapting therapeutic interventions. However, they are able to unmask ischemia in brain regions which are routinely not reached by standard monitoring techniques such as the brain stem or basal ganglia and assess concomitant metabolic alterations (SPECT, PET) and presence as well as differentiation of vasogenic/cytotoxic brain edema (CT, MRT) MRI.

To date, we still lack an easy-to-use and safe bedside tool with which cerebral perfusion can be assessed and most importantly quantified under routine intensive care conditions. We still must rely on indirect methods. In this context, SjvO_2 , ptiO_2 , and microdialysis play important roles. A further noninvasive tool is the transcranial Doppler/Duplex sonography with which flow velocity is determined in intracranial cerebral arteries and extracranial arteries. The absolute flow velocities in combination with the calculated Lindegaard ratio, the pulsatility, and resistance indices can be used to assess vasospasm and hyperemia, thereby allowing to adapt posttraumatic

therapeutic interventions [81]. [Calculation of the Lindegaard ratio, i.e., mean flow velocity in the mean cerebral artery divided by mean flow velocity in the internal carotid artery (ICA), requires adequate identification of the ICA, which is difficult in patients in whom the carotid bifurcation is hidden behind the mandible or cervical injuries preclude adequate positioning of the ultrasound transducer). Detailed investigations of cerebral autoregulation using TCD, assessing ICP and CPP, and considering calculated ICP/MABP ratio allow to unmask disturbances in vascular adaptation processes [84]. This is important whenever cerebral vessels are not able to adequately constrict or dilate. Thus, blood volume passively follows changes in arterial blood pressure, reflecting disturbed cerebral autoregulation. Elevating MABP can increase cerebral blood volume and thus elevate ICP, which in turn can impair cerebral perfusion. This is related to the loss in normal vasoconstriction. A decrease in MABP reduces cerebral perfusion due to absent vasodilation. While this reduces ICP cerebral perfusion is impaired concomitantly. Some patients suffer from a partially disturbed autoregulation as decreasing MABP (or CPP) results in an increase in ICP. This is a normal response as cerebral vessels dilate. However, the subsequent autonomic vasoconstriction reflex is lost. This, however, can be triggered by increasing MABP and CPP to the individually required level at which vasoconstriction occurs. At the bedside this results in a decrease in ICP, thus allowing to define required and individual CPP targets. This changes and normalizes over time, allowing to lower CPP again without increasing ICP.

Furthermore, disturbed cerebral autoregulation is also unmasked by characteristic changes of the ICP curve as the second peak exceeds the first peak, reflecting hampered autonomic vasoconstriction to the travelling arterial pressure wave. This can be simply diagnosed at the bedside on the monitor screen but requires a very good ICP curve. It is important to know that these alterations can occur several times per hour per day, and can persist for 1–2 weeks.

Combining TCD, ptiO_2 , and SjvO_2 allows to control and adapt therapeutic interventions and thus reduce the risk of inducing additional damage. In this context, elevated flow velocities (e.g., mean flow velocity within the MCA > 90 cm/s) together with elevated $\text{SjvO}_2 > 80\%$ and ptiO_2 values > 30 mmHg are suggestive of hyperemia. Thus, hyperventilation

and reduction in MABP and CPP to, for example, 50–70 mmHg can be indicated. Extremely elevated mean flow velocities in the MCA exceeding 120 cm/s with concomitantly reduced SjvO_2 and ptiO_2 are suggestive of vasospasm and requires imaging before hypoventilation and increase in CPP to 80–100 mmHg is performed. It is also important to adapt these interventions according to changes in ICP, especially in the presence of interhemispheric differences, i.e., signs of vasospasm on the one hand and concomitant hyperemia on the other. Correcting vasospasm on the one hand would aggravate hyperemia on the other hand and vice versa. An increase in ICP limits the induced interventions to avoid active induction of secondary brain damage (Fig. 2.18).

2.4.7.1 Crucial Points and Pearls

- Cerebral perfusion deficit induces secondary brain damage and thus must be prevented.
- Direct assessment of cerebral perfusion is still difficult and must be based on indirect measures such as SjvO_2 , ptiO_2 , metabolic changes (microdialysis), and TCD.
- Alterations in perfusion result from disturbed vasomotion, leading to hyperemia (maximal vasodilation) and vasospasm (vasoconstriction) with individual temporal profiles.
- These individual profiles afford individually adapted and controlled therapeutic interventions.

2.5 Therapeutic Interventions

Treatment of patients with severe TBI should only be performed in centers with well-trained interdisciplinary working teams experiencing at least 30 patients with severe TBI annually [82]. In addition, internal quality controls should be used to define own treatment protocols considering experiences of others and official guidelines. Main emphasis should be put on dynamic changes of the different pathologic/pathophysiologic changes and deteriorations as well as the pharmacodynamic and therapeutic effects of the induced interventions. It is also important that the standardized treatment concept remains flexible without becoming inconsistent. Rigid and categorical

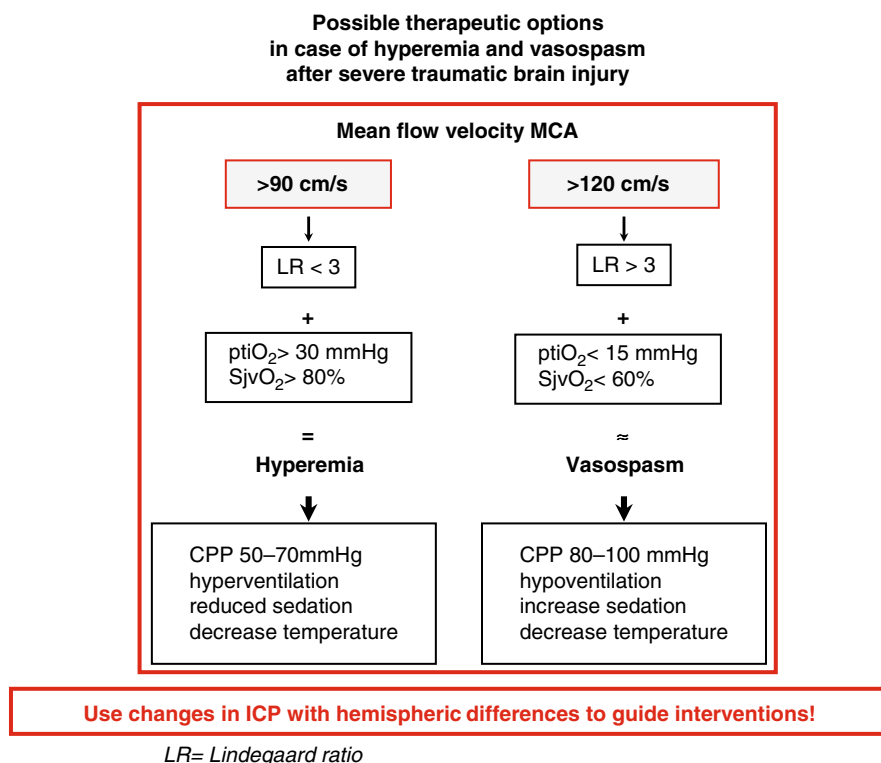


Fig. 2.18 Interplay of different parameters using color-coded duplex sonography of the middle cerebral artery (MCA) and internal carotid artery (ICA) including calculation of the Lindegaard ratio (LR = mean flow velocity MCA/mean flow velocity ipsilateral ICA) and measurement of jugular venous oxygen saturation (SjvO₂) and/or tissue oxygenation (ptiO₂) allow to differentiate hyperemia and vasospasm. This, in turn, can be used to guide differentiated therapeutic interventions, thereby preventing wrong and possibly damaging interventions. It is important to remember that patients can also suffer from heterogeneous distur-

bances. In this context, different flow velocity profiles can be measured on both sides which require diametral treatment: hyperemia versus vasospasm. Here the degree of therapeutic interventions must be guided by increases in intracranial pressure (ICP) to avoid iatrogenic secondary brain damage. Should an increase in cerebral perfusion pressure (CPP) be required to treat vasospasm this should not aggravate concomitant hyperemia, which, in turn, would elevate ICP. SjvO₂, ptiO₂, and microdialysis can be used for subsequent fine-tuning as these methods allow to unmask and define pathologic ICP and CPP values

orders carry the risk of exaggerated treatment which can induce and aggravate secondary brain damage. Furthermore, we must avoid a brain-centered treatment concept which does not consider other organ systems, thereby putting them at stake. A brain-oriented treatment concept considering different effects on all organs is preferred over a brain-centered approach. The different official guidelines – which are not written in rock – [83, 84] provide valuable input regarding how to treat patients with severe TBI. However, local facilities, diagnostic and therapeutic possibilities, as well as the conviction and knowledge of the treating team members are driving forces which strongly impact principal guidelines – influences which cannot be controlled on a broad basis. Principal therapeutic interventions are characterized in detail in the following subchapters.

2.5.1 Crucial Points and Pearls

- Therapeutic interventions must be flexible, and at the same time consistent and not dogmatic.
- A brain-oriented therapy under consideration of potential harm to other organ systems is preferred to a brain-centered treatment concept.
- Official guidelines are recommended and are strongly impacted by local influences and personal knowledge and conviction of the treating physicians.

2.5.2 Positioning

To improve cerebral venous outflow and to reduce increased ICP due to venous congestion it is important

to identify optimal positioning of the individual patient. As with many aspects in modern intensive care positioning should not be dealt with categorically since also other organ systems such as lungs and intestines show their own dynamic changes with their individual needs. This must be considered as well. Clinical experience shows that elevating the upper part of the body to 30° as suggested in the guidelines does not always reduce elevated ICP. Thus, the optimal positioning must be searched anew daily and during the individual day. Optimal positioning can range from 0° to 30°, and even more. In addition, patients can profit from positioning themselves on their side and individual side preference must also be remembered. The type of the used pillow or ring can trigger occipital neuralgic points which can increase blood pressure and also elevate ICP.

2.5.2.1 Crucial Points and Pearls

- Optimal positioning (elevation of the upper part of the body, lateral rotation) must be individualized.
- Positioning must be adapted to the clinical situation.

2.5.3 Oxygenation

The metabolically active brain must be supplied with sufficient amounts of oxygen to fuel the oxygen-consuming processes. For this, a sufficient cardiac output with an optimal perfusion and an adequate hemoglobin concentration are required to enable ideal oxygen transport and cerebral oxygen supply. This again requires intact cardiac and pulmonary functions to attain an adequate increase in physically bound and dissolved oxygen in blood. Pulmonary impairment due to atelectasis, pneumonia, and lung failure (acute lung injury (ALI)/acute respiratory distress syndrome (ARDS)) reduces SaO_2 and paO_2 . This, in turn, decreases cerebral oxygen supply with the risk of secondary brain damage.

Apart from a direct pulmonary damage which is observed following isolated experimental TBI [85] and in clinical routine [86] exogenous influences due to thoracoabdominal injuries are also discussed as possible reasons for evolving pulmonary impairment and failure. In addition, blood transfusions [87] and excessive infusion of crystalloids and colloids are thought to induce ALI/ARDS following TBI [88].

In lung protective ventilation a peak pressure > 35 mbar and a plateau pressure > 30 mbar must be avoided to prevent volume- and pressure-induced lung damage. Any additional injury leads to progressive damage and forms the basis for facilitated injury such as pneumonia. Ventilatory settings are defined by the predefined paO_2 target. Thus, if the paO_2 target is set too high, then increased positive end-expiratory pressure (PEEP) can induce disadvantageous structural and functional changes in lungs and circulation, especially during hypovolemia as an elevated PEEP will impair venous backflow to the heart and result in secondary reduced pulmonary perfusion with worse blood oxygenation [89, 90].

Cerebral oxygen requirement is reduced by sedation and hypothermia which increases the threshold for hypoxic damage, thereby protecting the brain. Consequently, it is important to monitor cerebral oxygenation by assessing changes in SjvO_2 and ptiO_2 , measuring metabolic changes by microdialysis, and by calculating metabolic indices (see Sect. 2.4.3). This again allows to adapt required paO_2 and actual ventilatory settings, thereby preventing unnecessary and potentially damaging therapeutic interventions. Empirical recommendation is to maintain paO_2 between 11 and 13 kPa, i.e., 83 and 98 mmHg. Using SjvO_2 and ptiO_2 values even lower paO_2 values can be tolerated under controlled conditions, thereby reducing any ventilatory-induced pulmonary stress and damage.

Increasing paO_2 to elevated levels by normobaric hyperoxygenation improves cerebral oxygen supply [54, 91] and ameliorates aerobic metabolism reflected by reduced lactate production [92]. However, normobaric hyperoxygenation is associated with an increased risk of inducing vasoconstriction [54] and promoting atelectasis [93] with pulmonary shunts. To date, normobaric hyperoxygenation cannot be recommended as a routine therapeutic intervention. The duration and extent of normobaric hyperoxygenation must still be defined.

2.5.3.1 Crucial Points and Pearls

- Cerebral oxygenation is crucial to avoid secondary brain damage.
- The actual and individual oxygen requirement which determines aggressiveness of ventilatory settings and transfusion threshold must be determined by SjvO_2 or ptiO_2 to prevent any excessive, unnecessary, and damaging therapeutic interventions.

- Normobaric hyperoxygenation is discussed controversially. Important details as indication, duration, and extent must still be defined before it can be recommended in clinical routine.

vasoconstriction. For this, changes in $SjvO_2$, $ptiO_2$, or metabolic parameters (microdialysis) are valuable tools with which individually acceptable $paCO_2$ limits can be identified, thereby avoiding induction of secondary brain damage.

2.5.4 Hyperventilation

Initially, prophylactic hyperventilation was thought to be an elegant way of reducing elevated ICP (Table 2.7). However, experience gained in the past years showed that uncontrolled and prophylactic hyperventilation during the early posttraumatic phase, i.e., the first 5 days induces additional secondary brain damage [94]. In this context, hypocapnia-induced vasoconstriction with impaired perfusion, metabolic and neurochemical alterations [95], and reduced $ptiO_2$ and $SjvO_2$ with elevated extracellular glutamate and lactate levels have been documented. Interestingly, even small changes in $paCO_2$ from 38 to 34 mmHg within normal limits is detrimental [96]. According to the official guidelines chronic hyperventilation must be avoided during the first 5 days and most importantly should not be used during the initial 24 h because cerebral perfusion is impaired predominantly during the first 24 h and any further reduction is a secondary insult, thereby aggravating underlying structural and functional damage. This, in turn, could increase lesion volume and aggravate cerebral edema and impair cerebral vascular reactivity, thereby disturbing cerebral autoregulation. In addition, hypocapnia can also induce negative systemic effects such as pulmonary vasodilation with intrapulmonary shunts and vasoconstriction of the coronary arteries with subsequent functional disturbances [6].

Whenever patients are hyperventilated to decrease elevated ICP, hyperventilation must be controlled using appropriate neuromonitoring techniques to unmask signs of cerebral deterioration due to hyperventilation-induced

2.5.4.1 Crucial Points and Pearls

- Hyperventilation can reduce elevated ICP due to induced vasoconstriction.
- Hypocapnia-induced vasoconstriction can induce cerebral ischemia and mediate secondary brain damage.
- Hyperventilation should always be controlled using $SjvO_2$, $ptiO_2$, or microdialysis; however, these parameters do not offer absolute protection against induced ischemia.
- While controlled hyperventilation can be used to treat underlying hyperemia, hypoventilation with corresponding vasodilation can be performed to treat vasospasm.

2.5.5 Analgesia and Sedation

Following severe TBI the brain is characterized by an increased vulnerability to influences which under normal conditions are not of pathologic importance. In this context, coughing and straining can elevate ICP due to impaired venous outflow and increased oxygen consumption. Uncontrolled hyperventilation due to pain or impaired vigilance can induce vasoconstriction, thereby aggravating secondary brain damage. These alterations can be suppressed by administration of analgetics (e.g., fentanyl, sufentanyl), hypnoanalgetics (e.g., ketamine), sedatives (e.g., benzodiazepines, barbiturates, propofol), and – if necessary – muscle

Table 2.7 Effects of different $paCO_2$ values

$paCO_2$	Indication	Effect	Unwanted cerebral effects
Normocapnia (35–45 mmHg; 4.6–5.9 kPa)			
Hypocapnia (<35 mmHg; <4.6 kPa)	Reduction in ICP	Vasoconstriction	Ischemia, infarct, ICP increase, <i>CAVE</i> : vasospasm
Hypercapnia (>45 mmHg; >5.9 kPa)	Improvement of: perfusion, oxygenation, metabolism	Vasodilation	ICP increase Disturbed autoregulation

relaxants (e.g., rocuronium, pancuronium, vecuronium, atracurium). Analgetics and sedatives decrease neuronal activity and thereby reduce cerebral metabolism and oxygen consumption. This, in turn, can reduce cerebral blood volume, thereby decreasing ICP. Consequently, analgetics, sedatives, and muscle relaxants can decrease elevated ICP.

To date, however, it remains elusive which drugs, at which dose, and in which combination are optimal [97]. While administration of single drugs carries an elevated risk of accumulation and prolonged context-sensitive half-life resulting in tolerance with subsequent loss of action, a combination of different drugs with different receptor targets could reduce these unwanted side effects as performed in the “Lund concept.” This, in turn, could allow to reduce the dose of the individual drugs.

It also remains unclear whether different traumatic brain lesions influence pharmacodynamic properties of different drugs [98].

Continuous infusion of propofol has the advantage of allowing a faster awakening since its half-life is significantly shorter compared to benzodiazepines and barbiturates (hours vs. days). However, propofol induces more severe hemodynamic instability. In addition, propofol can induce the lethal “propofol-infusion syndrome,” characterized by lactic acidosis, rhabdomyolysis, renal insufficiency/failure, arrhythmias, and cardiac failure [99]. Consequently, propofol should be limited to a maximum of 4 mg/kg body weight/h and for a maximum of 4 days; infusion duration, however, is discussed controversially.

In many centers daily wake-up trials are conducted to perform neurological evaluations. For this, analgetics and sedatives are stopped irrespective of the local changes and the overall condition of the patient. Only patients with minor TBI might exhibit normal arousal reaction. Patients with severe TBI will not show an adequate reaction compared to arousal from short anesthesia. Clinically, patients will react with a vegetative storm consisting of hypertension, tachycardia, hyperventilation, hyperhidrosis, hypersalivation, maybe diarrhea, and extreme agitation. These alterations are secondary insults and can induce secondary brain damage. Following such a wake-up trial re-sedation can be very difficult since this excessive excitation observed under conditions of drug withdrawal is associated with functional alterations of various receptor subtypes. According to our experience awakening should only be performed when signs of cerebral edema have completely resolved

on CT scan. As long as brain edema persists, the injured brain is extremely vulnerable to secondary insults. Analgetics and sedatives should be reduced slowly and under controlled conditions to avoid vegetative withdrawal reactions. Withdrawal reactions result from pharmacologic tolerance due to functional alterations of various receptors induced by prolonged sedation and reflects addiction [99]. Vegetative withdrawal symptoms: hyperventilation, tachycardia, hypertension, hypersalivation, hyperhidrosis, and diarrhea can be treated with continuous clonidine infusion. However, clonidine-induced bradycardia and hypotension can limit its administration. Agitation can be treated with continuous infusion of propofol (<4 mg/kg/h). During continuous administration of clonidine/propofol opioids and benzodiazepines can be reduced [100]. With signs of intracranial deterioration reflected by, for example, decreased $SjvO_2$ the wake-up phase must be interrupted by either discontinuing further drug reduction or by increasing the depth of sedation for 12–24 h before continuing controlled drug reduction.

2.5.5.1 Crucial Points and Pearls

- Analgesia, sedation, and cautious administration of muscle relaxants can protect the brain from secondary insults and are important in treating patients with severe TBI.
- To date, it remains elusive which drugs, at which dose, and which duration are optimal.
- Abruptly stopping analgesia and sedation should be avoided as this can induce uncontrollable vegetative reactions (hyperventilation, hypertension) which can additionally damage the brain.
- As long as brain edema persists the brain is vulnerable and secondary insults must be avoided.
- To treat vegetative withdrawal symptoms and motoric agitation resulting from tolerance and addiction due to prolonged administration of analgetics and sedatives, clonidine and propofol can be used; clonidine and propofol do not induce addiction, tolerance, or withdrawal symptoms by themselves.

2.5.6 Optimal Hematocrit and Transfusion Requirements

To prevent posttraumatic ischemic and hypoxic secondary insults adequate perfusion and adequate oxygen supply

must be achieved. Oxygen supply is mainly mediated by oxygen bound to hemoglobin and cardiac output. To provide sufficient oxygen to the brain an appropriate number of oxygen carriers, i.e., red blood cells, must be present. However, it remains unclear which red blood cell count, reflected by the hematocrit, is optimal in patients with severe TBI. This is especially difficult since regional as well as temporal heterogeneous pathophysiologic changes have different requirements.

From a physiologic point of view any hematocrit is optimal at which the tissue is sufficiently supplied with oxygen without reducing perfusion due to increased viscosity. According to Gaehtgens and colleagues [101] there is a nearly linear relationship between hematocrit and cerebral perfusion: while decreased hematocrit improves microcirculatory perfusion, microcirculation is impaired at higher hematocrit levels. Concomitantly, however, cerebral oxygen supply shows a U-shaped reduction with a significant worsening at hematocrit <30% and >50%. This janus-faced characteristic profile is explained by the changes in viscosity and the reduction in oxygen carriers. In this context, reduced hematocrit decreases viscosity, which in turn increases blood flow according to the law of Hagen–Poiseuille since viscosity shows an inverse relation to blood flow ($Q = P\pi r^4/8L\eta$, with Q = blood flow, P = pressure gradient, r = vessel radius, L = vessel length, η = viscosity). Increased blood flow, in turn, could induce normal vasoconstriction, which, following severe TBI, however, could impair cerebral perfusion and decrease oxygen supply. Elevated hematocrit, which rarely exceeds 50% under clinical conditions, increases viscosity and thereby decreases blood flow. Thus, the microcirculatory perfusion is slowed and risk of local thrombosis is increased. Vasodilation to overcome decreased blood flow increases ICP, which in turn can aggravate underlying disturbed microcirculation.

Inducing acute hemodilution with a hematocrit < 21% under experimental conditions resulted in damaging effects [102, 103]. In patients with preexisting vasospasm following ruptured aneurysm bleeding, active reduction in hematocrit from 36% to 28% resulted in significantly reduced cerebral oxygen supply [104]. Thus, any form of severe hemodilution should be avoided. However, detailed cerebral effects of slow or fast reduction in hematocrit following severe TBI have not been investigated yet [105].

Overall, it remains unclear which absolute hematocrit value can be considered adequate, and which

relative changes in which time interval and at which time point will induce negative effects. In addition, it remains unclear if reduction in brain temperature, deep sedation, and elevated CPP are neuroprotective in cases of low and high hematocrit levels under clinical conditions. In theory, hypoxic threshold is increased whenever brain metabolism is reduced by hypothermia and deep sedation, thereby allowing a lower hematocrit level and thus decreasing transfusion requirement.

Under stable critical care conditions with stable CPP and stable oxygenation and ventilation it was recently shown that transfusion of red blood cells influences $ptiO_2$ in approximately 75% of the investigated patients [55, 106]. Interestingly patients with a $ptiO_2 > 15$ mmHg do not profit from red blood cell transfusion, suggesting that $ptiO_2$ can be used to continuously assess critical transfusion threshold. Further investigations, especially related to the age of transfused red blood cells, are required [107] as older red blood cells (storage exceeding 2 weeks) show an impaired oxygen-carrying capacity.

The current official recommendation based on a post hoc analysis is that hematocrit values can be maintained at values between 21% and 27%, i.e., during stable critical care conditions [108]. However, only an adequate prospective study will allow to decide whether the suggested hematocrit range of 21–27% can be tolerated in all patients as suggested by the Transfusion Requirements in Critical Care (TRICC) study [109]. In addition, appropriate outcome parameters, such as continuously measured $ptiO_2$, must be included to unmask dynamic changes of the transfusion threshold. This is required to adequately reduce TBI-related mortality and morbidity, to also prevent unnecessary transfusions which contribute to increased mortality and morbidity, and to avoid missing required transfusions.

The search for an optimal hematocrit is also associated with the task of optimizing plasmatic and thrombocytic coagulation parameters since ongoing bleeding will also increase mortality and morbidity. Under stable clinical conditions, platelets > 80,000/ μ L, INR < 1.4, fibrinogen > 1.5 mg/dL, and ionized calcium > 1.2 mmol/L are required.

2.5.6.1 Crucial Points and Pearls

- Optimal cerebral oxygen supply is essential to avoid secondary brain damage.

- To date, it remains elusive which hematocrit following severe TBI is optimal.
- Further analysis is indispensable to characterize differential needs in different phases and to possibly define phase-specific requirements in cerebral oxygenation and transfusion thresholds. For this, continuous measurement of ptiO_2 and metabolic parameters (microdialysis) could be of significant help.
- Regular controls of coagulation parameters are important to unmask and correct disturbed plas-matic and thrombocytic coagulation.

2.5.7 Optimal Blood Glucose Values

Elevated blood glucose levels >9.4 mmol/L (>169 mg/dL) are associated with increased mortality and morbidity [110–114]. During the early phase elevated blood glucose levels reflect the degree of underlying damage and severity of initial stress characterized by corresponding sympathoadrenergic activation. Thus, other pathophysiologically important cascades must also be considered. Hyperglycemia induces mitochondrial damage, aggravates oxidative stress, impairs neutrophil function, reduces phagocytosis, and diminishes intracellular destruction of ingested bacteria. Thus, fast correction of elevated blood glucose levels and normalization should be achieved [115] (Table 2.8). However, it still remains unclear which blood glucose values are optimal. While the group of van den Berghe propagates a protective effect of low normal blood

glucose levels between 4.4 and 6.1 mM (80–110 mg/dL) due to reduced morbidity and mortality and decreased hospitalization and its cost effectiveness [116] other groups as well as van den Berghe herself could not reproduce these data in other patients [117–119]. In this context, it is important to acknowledge that the potentially positive effects are not seen until 3–5 days of reduced blood glucose levels. During the first days, however, mortality was even increased upon reducing arterial blood glucose levels [116–118], which is attributed to the increased frequency of hypoglycemia. Despite adhering to a strict protocol which included continuous glucose infusion, hypoglycemic episodes could not be prevented by van den Berghe and colleagues. Absolute and relative hypoglycemic episodes are secondary insults that must be avoided. As shown by Vespa and coworkers reducing blood glucose levels to 4.4–6.1 mmol/L results in significant metabolic and energetic cerebral impairment of the traumatized brain [120]. Apart from elevating extracellular glutamate levels lactate/pyruvate ratio was also significantly increased, reflecting excessive neuronal excitation and metabolic perturbation. In addition, mortality was increased in patients with decreased blood glucose and low cerebral extracellular glucose levels [121]. Under experimental and clinical conditions blood glucose levels <5 mmol/L can induce spontaneous cortical depolarizations (CSD) [12, 76, 122]. Thus any correction to low blood glucose values should be tightly monitored including specific cerebral monitoring such as microdialysis and jugular venous BGA to avoid inducing additional damage and to also

Table 2.8 Effects of reducing blood glucose levels using intensified insulin therapy

Positive effects	Negative effects	Brain-specific effects
Reduce critical illness polyneuropathy	Hypoglycemia	Reduced glucose levels
Attenuate renal injury	Hyperglycemia	Increased glutamate levels
Reduce pneumonia/pulmonary damage	Tight controls, repetitive blood sampling	Elevated lactate/pyruvate ratio
Decrease blood cortisol	Increased insulin requirement	Increased O_2 extraction
Reduce morbidity/mortality		
Improved cellular and humoral immunocompetence	Elevated costs	Increased CSD
Improved mitochondrial function		Reduced ICP
Protect endothelial cells		Attenuated norepinephrine requirement
		Reduced seizures
		Diminished diabetes insipidus

facilitate identification of optimal blood glucose values in face of temporal and regional heterogeneous glucose consumption [37, 123–128]. Reducing cerebral glucose supply by decreasing arterial blood glucose can induce secondary brain damage, which is aggravated by concomitantly reduced cerebral perfusion. Induced activation of glucose transporters, e.g., GLUT 1, can provoke additional brain damage as increased activation of these transporters amplifies oxygen deficit created by insufficient blood glucose levels. This, in turn, will increase extracellular glutamate levels, which induces neuronal and glial damage. These cascades can also be provoked by undulating blood glucose levels (Fig. 2.19). Recent data suggest that patients might profit from low blood glucose concentrations in the second posttraumatic week [129]. At present, however, it is unclear whether these beneficial effects are also seen if blood glucose levels are decreased in the second week by intensified insulin administration or whether these effects can only develop over time, thereby requiring early administration during the first and highly vulnerable week.

While the pathologic upper blood glucose limit of 10 mmol/L (180 mg/dL) has been clearly defined, the lower blood glucose limit must still be determined. Based on retrospective analysis arterial blood glucose levels should neither drop below 4 mmol/L (72 mg/dL) nor exceed 9 mmol/L (162 mg/dL) [30]. As a compromise blood glucose values could be maintained between 6 and 8 mmol/L (108 and 144 mg/dL), a range with the highest cerebral metabolic stability.

2.5.7.1 Crucial Points and Pearls

- Persisting hyperglycemia (>10 mmol/L, >180 mg/dL) increases morbidity and mortality.
- Correction and normalization of elevated blood glucose levels is essential.
- Normalization of elevated blood glucose levels to 4.4–6.1 mmol/L (80–110 mg/dL) induces hypoglycemia and undulating blood glucose levels, thus increasing morbidity and mortality.

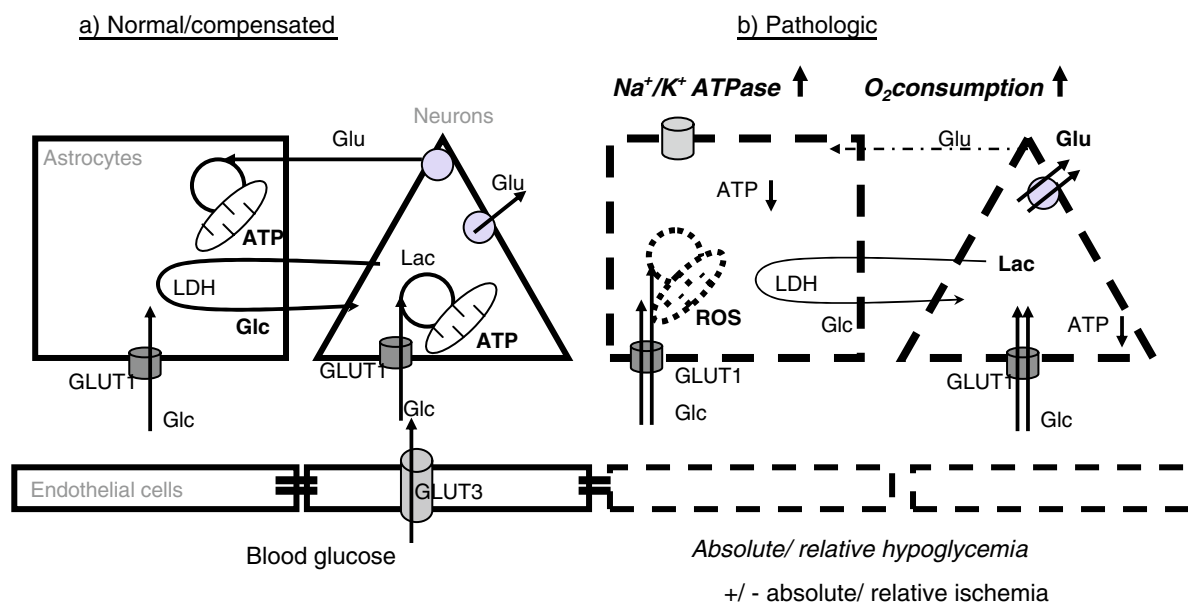


Fig. 2.19 Schematic drawing of physiologic influences of cerebral glucose uptake and intracellular metabolism and glial-neuronal interactions (a) and pathophysiologic changes induced by systemic hypoglycemia (b). Sustained expression and increased activity of specific glial and neuronal glucose transporters mediate intensified glucose uptake even in the face of low extracellular glucose levels. This compensation, however, only

insufficiently satisfies underlying growing energetic requirements. The increased oxygen consumption, in turn, results in an oxygen deficit and insufficient adenosine triphosphate (ATP) production. As a consequence, glutamate uptake is reversed resulting in increased extracellular glutamate. The elevated lactate/pyruvate ratio reflects mitochondrial impairment. Undulating blood glucose levels are feared to aggravate induced cascades

- Those patients must be identified in whom blood glucose levels can be reduced to 4.4–6.1 mmol/L without any additional risks to avoid endangering other patients who will not profit from the intensified insulin treatment.
- A time dependent optimal blood glucose target must still be defined.
- Until new convincing and safe data have been obtained maintaining arterial blood glucose levels between 5 and 8 mmol/L appears to be a safe compromise.
- Improved continuous blood glucose control using a computer-supported automatized insulin administration could facilitate maintenance of stable low blood glucose levels, thereby avoiding damaging hypoglycemic episodes and undulating blood glucose concentrations.

2.5.8 Barbiturate Coma

Barbiturates, depending on concentration, suppress cerebral metabolism and oxygen consumption by activating the neuronal GABA/Cl⁻ receptor channel independently of the inhibitory transmitter GABA. The degree of metabolic suppression strongly depends on the initial level of activation [130]. Overall, reduction in cerebral oxygen consumption decreases intracranial blood volume and improves cerebral autoregulation [131]. In addition, diminished glutamate release and metabolic stabilization were reported [66, 132]. These different effects reduce elevated ICP, which, however, is not observed in all patients to the same extent.

Due to various dose-dependent side effects (hypotension due to cardiac depression, cellular immunosuppression, bone marrow insufficiency, and increased rate of pneumonia) barbiturate coma using a high dose with the induction of 3–6 bursts/min is not seen as a first-tier therapeutic intervention. According to the official guidelines prophylactic barbiturate coma is discouraged as it may increase mortality and morbidity [133]. However, the data were predominantly obtained at a time when intensive care treatment did not meet contemporary standards. One major problem is the barbiturate-induced arterial hypotension due to cardiac depression and barbiturate-induced adrenal insufficiency with consecutive hypotension, which contributed to an increased mortality as shown

in a COCHRANE meta-analysis [134, 135]. In modern intensive care, such barbiturate-induced changes can be corrected easily by infusing appropriate amounts of fluids and by administering vasopressors and inotropics guided by appropriate monitoring tools such as a pulmonary artery catheter or Picco® System. In addition, patients suffering from severe TBI were maintained hypovolemic and received osmotherapeutics on a regular basis and were subjected to prophylactic hyperventilation, which could have provoked deleterious vasospasm that was neither searched for actively nor treated adequately. Furthermore, barbiturate coma induces hypothermia, which per se can induce immunosuppression and coagulopathy, and increase risk for infections. In addition, other important therapeutic and diagnostic interventions have improved in the past decades, which prevents a direct comparison. The official guidelines which propagate a reluctant position in administering barbiturates are challenged by the “Lund-concept” (s. X.Y) (2.5.12.2, p. 39) in which thiopental is infused continuously at a low dose (0.5–3 mg/kg/h compared to the high-dose thiopental as used for barbiturate coma at 6–10 mg/kg/h) in addition to other sedatives and analgetics, e.g., fentanyl, midazolam, clonidine, metoprolol. These different drugs with their different receptor targets are infused in parallel.

Furthermore, the inclusion criteria to begin barbiturate coma if ICP > 30 mmHg for longer than 30 min in addition to a CPP < 60 mmHg or ICP > 40 mmHg despite a CPP > 60 mmHg might be wrong as these indications result in a late start of barbiturate. Thus, secondary brain damage has already occurred which is extremely difficult to treat and manage once it has developed.

2.5.8.1 Crucial Points and Pearls

- Barbiturate coma may reduce therapy-refractory increase in ICP in some patients.
- Barbiturate coma requires detailed invasive hemodynamic monitoring and adequate correction of cardio depression, vasodilation, and adrenal suppression.
- An increased vigilance for infections is also important.
- Contrary to the high dose as used for the conventional barbiturate coma low dose as applied within the “Lund-concept” could be related with less side effects.

2.5.9 Temperature, Fever, Hypothermia, Rewarming

Based on experimental and clinical data increased body temperature exceeding 38.5°C, corresponding to 40–41°C in the brain, induces destructive biochemical cascades leading to structural and functional deficits, which, in turn, aggravate posttraumatic mortality and morbidity [135]. As long as cerebral oxygen supply and cerebral perfusion are optimal fever does not seem to induce metabolic perturbation. Cerebral vasodilation, however, can elevate ICP [136]. Thus, an increase in temperature should be avoided and normo- or even moderate hypothermia should be induced. Reducing temperature by 1°C reduces cerebral oxygen consumption by approximately 5%. To date, it still remains unclear which target temperature should be induced and for how long this temperature should be maintained. While an American multicenter study could not provide convincing evidence of maintaining hypothermia of 32–33°C during the first 24 h [137] other studies were able to demonstrate significant benefits [138, 139]. In children, however, early hypothermia was even associated with increased mortality [140].

To date, target temperature, site of measuring temperature, time point of inducing and duration of maintaining hypothermia, as well as means of cooling and speed of rewarming are discussed controversially.

While some centers primarily target normal body temperature (37–38°C) and only start reducing temperature once ICP increases, other centers initially induce mild hypothermia with a brain temperature of 35–36°C even at normal ICP levels. Moderate hypothermia at 33–35°C is usually accepted as a side effect of barbiturate coma.

The site at which temperature is measured is also discussed controversially. While most centers measure temperature rectally, auricular, in the bladder, in the jugular venous bulb (using a pediatric pulmonary artery catheter), in the artery, or in the pulmonary artery, only few centers determine brain temperature directly. Since brain temperature can exceed temperature determined at other sites by as much as 2°C it is obvious that effects of temperature not determined within the brain will be underestimated. The newer generation of ICP probes possesses an integrated temperature sensor. Alternatively, separate temperature sensors can be inserted in addition to the ptiO₂ probe.

The manner in which patients are cooled can range from the conventional, noninvasive, and cheap but difficult-to-control surface cooling using cooling mats to the sophisticated, invasive, and expensive but very easy-to-control intravenous cooling using, for example, Intravascular Temperature Management (IVTM™) (www.alsius.com) [141]. New data propagate noninvasive cooling with the Arctic Sun® 2000 Temperature Management System (www.medivance.com) [142].

Other cooling methods such as selective cooling of the head using a specialized helmet or reducing temperature of the cervical vessels are currently being investigated.

Pharmacologic reduction in temperature using paracetamol and metamizol is widely performed but must be viewed critically and cautiously due to potential severe side effects such as hepatic toxicity and neutropenia.

Rewarming should be performed slowly and controlled by adequate cerebral monitoring. In this context, a speed of rewarming ranging from 1°C/12 h to 1°C/24 h is recommended. Fast rewarming can induce generalized vasodilation with systemic hypotension and disturbed cerebral autoregulation resulting in elevated ICP and metabolic perturbation [143]. Due to individually different responses adequate neuromonitoring is required to control and specifically guide the rewarming process.

2.5.9.1 Crucial Points and Pearls

- Fever induces cerebral secondary damage and must be avoided.
- Reducing brain temperature decreases cerebral metabolism.
- To date, target temperature, duration, and means of reducing temperature remain elusive.
- Early hypothermia with 32–34°C during the first 2 days is associated with an increased mortality and thus cannot be recommended.
- Pharmacologic reduction in temperature must be performed cautiously or even avoided due to possible severe side effects.
- Rewarming must be performed slowly and with appropriate neuromonitoring to avoid inducing secondary brain damage due to systemic hypotension and disturbed cerebral autoregulation with subsequent elevated ICP.

2.5.10 Hemodynamic and Volume Management

Cerebral perfusion as well as perfusion of all organ systems depends on sufficient cardiac output. Nearly all patients with severe TBI exhibit hypotensive blood pressure values even in the absence of hemorrhage, regarded as a side effect of analgesia/sedation and the trauma-induced severe systemic inflammatory response syndrome, which increases endothelial permeability and thus induces volume shift and volume loss into the “third space.” To prevent this hypovolemia from becoming a secondary insult and to prevent it from inducing secondary brain damage, volume must be infused for hemodynamic stabilization. Ideally, we should achieve an optimal volume status. In reality, however, it is difficult to reach and maintain euvoolemia/normovolemia. The goal is to prevent excessive volume administration, as is discussed, to increase the risk of ARDS [144] and abdominal compartment syndrome [145]. Volume management becomes difficult in septic and bleeding patients in whom prolonged activation of the inflammatory system is associated with an increased volume requirement. In the early phase, a negative fluid balance should be avoided since this is associated with an increased risk of developing cerebral vasospasm and results in an elevated need of catecholamines which will induce organ damage in the face of underlying hypovolemia.

To date, the type of fluid to be administered is discussed controversially. While some countries predominantly use Ringer Lactate or NaCl 0.9%, other countries infuse modern, i.e., balanced crystalloid, solutions in combination with balanced colloid solutions. NaCl as well as glucose solutions should be avoided as severe side effects can induce additional organ damage related to hyperchloremic acidosis (NaCl) and edema promotion and tissue acidosis (glucose solutions). The benefits of the novel balanced solutions must be evaluated in clinical routine.

Apart from volume administration infusion of vasoconstrictors and inotropics are important. In principal, a balance between volume administration and pharmacologic hemodynamic support must be found to prevent excessive administration of catecholamines with the aim of reducing volume load as this can induce organ damage similar to the consequences of volume overload by itself. To date, we are lacking an international consensus regarding which vasoconstrictors are to be used. While many centers use norepinephrine, others administer the synthetic vasopressor phenylephrine and some use ket-

amine, which is known to increase arterial blood pressure due its norepinephrine-releasing effect [146].

Control of hemodynamic and volume management is based on different parameters which can be observed easily, e.g., MABP including the curve form (which requires invasive blood pressure measurement), heart rate, diuresis including color of urine, sodium and osmolality in urine, and to a certain extent central venous pressure. For a more detailed guidance including administration of inotropics (e.g., dobutamine) invasive methods are required such as the Picco® system or a pulmonary artery catheter. As a compromise and until these catheters have been introduced central venous oxygen saturation (ScvO₂) can also be used. A ScvO₂ < 60% suggests a reduced cardiac output resulting in an impaired perfusion of various organs which can be corrected by dobutamine administration and volume infusion. During deep analgesia/sedation, barbiturate coma, and controlled hypothermia ScvO₂ can only partially be used due to the generalized decrease in oxygen consumption which increases ScvO₂ values.

During hemodynamic management, vasopressor-induced refractory bradycardia can decrease cardiac output and thus impair cerebral perfusion. This can be corrected easily by reducing pharmacologic vasoconstriction and infusing dobutamine. This, however, requires active measurement of cardiac output to differentiate bradycardia. Bradycardia can also result from extensive exercise in athletes, can reflect sick-sinus syndrome, or can result from hypothermia as well as deep analgesia/sedation.

Dysrhythmia can result from hypokalemia, hypophosphatemia, and hypomagnesemia, which must be corrected. Regular electrocardiogram (ECG) controls are indicated for early diagnosis of a prolonged QT-interval which can be corrected by infusing magnesium.

Depending on the severity of the trauma and the trauma-induced extent of sympathoadrenergic activation, signs of subendocardial ischemia can be seen in routine ECG.

2.5.10.1 Crucial Points and Pearls

- For adequate hemodynamic support with the aim of maintaining optimal cerebral perfusion volume, catecholamines, and inotropic agents must be combined. To date, there is no international consensus concerning which drugs are to be used.

- Hemodynamic and volume management must be adjusted to the individual needs to prevent organ damage.
- Periodic ECG controls are important to diagnose cardiac ischemia, arrhythmia, and prolonged QT time, and daily electrolyte controls are essential in preventing arrhythmia and guiding their treatment.

2.5.11 Osmotherapy: Mannitol, Small Volume Resuscitation, Albumin

Concentration-dependent changes predominantly of sodium and alterations in the osmotic gradient across the blood brain barrier contribute to the development and resolution of brain edema. Consequently, influencing the osmotic gradient is a sensible and useful therapeutic option to treat brain edema. In this context, mannitol and hypertonic NaCl solution with and without dextran have been investigated under clinical conditions [147, 148] (Table 2.9).

Due to its strong osmotic effect mannitol expands the blood volume, decreases the hematocrit and reduces blood viscosity. In addition, cerebral perfusion and cerebral oxygen supply are improved rapidly. These effects require a CPP > 70 mmHg and reduced serum osmolality. At an increased serum osmolality above 320 mOsmol/L, which is predominantly induced by elevated sodium levels, mannitol should not be infused. Continuous mannitol infusion is thought to possibly aggravate edema formation and thus increase ICP whenever the blood brain barrier is damaged. A severe and eventually organ-damaging side effect is the induced osmotic diuresis resulting in hypovolemia and electrolyte disturbance. This hypovolemia can

increase systemic lactate levels, which is observed in patients who are craniectomized in time due to cerebral herniation who then develop diabetes insipidus resulting from herniation-induced pituitary/hypothalamic ischemic injury. In addition, osmotic nephropathy is feared [149] as recently reported concentration effects resulting from the anti-edematous action could impair cerebral function [150].

As concluded in the recently published COCHRANE analysis, mannitol lacks sufficient evidence to be recommended for routine clinical use [147]. This, however, does not mean there are insufficient indications and does not exclude a search for clear definitions for the controlled application of mannitol such as for therapy-refractory elevations in ICP with herniation signs at normal serum osmolality.

An alternative to mannitol is seen in hypertonic NaCl solutions in terms of small volume resuscitation (SVR). For this, a small volume of usually 4 mL/kg of a 7.2–7.5% NaCl/colloid solution is infused within 5–10 min. Due to the rapid volume expansion related to the osmotic strength of SVR it is mainly the hypotension which is corrected. In a double-blind placebo-controlled trial SVR corrected hypotension without, however, improving mortality and morbidity [151]. Due to the reduced penetration of the blood brain barrier and the anti-edematous action in injured brain regions [152] these osmotherapeutic agents might also qualify as a treatment option for elevated ICP during the ICU phase. Further positive effects are found in improved perfusion at increased vessel diameter resulting from induced tissue dehydration [17]. In addition, hypertonic NaCl solution counteracts glutamate-mediated toxicity by stabilizing cell membranes and reduces infectious complications related to different immunomodulatory effects. Apart from these positive

Table 2.9 Osmotherapy

Compound	Indication	Main effect	Side effects
Albumin (4%, 20%)	Correct plasma albumin, aim > 20 g/dl	Constant colloidosmotic potency, reduce brain edema	Osmotic nephropathy with tubulus injury
Mannitol (20%)	ICP reduction, Serum osmolality <320 mOsmol/kg	Osmotic potency, volume expansion, increase in cerebral perfusion	Osmotic diuresis with electrolyte disturbance Osmotic nephropathy Hypervolemia with pulmonary edema
Hypertonic NaCl-solution (7.2–7.5%) Hypertonic NaCl with dextran	ICP reduction Serum osmolality < 320 mOsmol/kg	Osmotic potency, volume expansion	Hypernatremia, hemorrhage, central pontine myelinolysis Hyperhydration

actions rebound increase in ICP following termination of continuous infusion of hypertonic NaCl solutions must be considered which could induce local and systemic injuries. In this context, central pontine myelinolysis due to rapid changes in sodium, renal failure, dilution coagulopathy, cardiopulmonary failure due to hypervolemia, and hemorrhages induced by hypertension may occur.

Overall, potency of reducing frequency of therapy-refractory increases in ICP due to SVR appears to be superior to mannitol [153]; mortality and morbidity, however, remain uninfluenced. However, the significant difference in osmotic composition of the different solutions (350 vs. 175 mOsmol) reduces the validity of these results. In a recently published study designed to investigate short-term effects within the first 120 min, the actions of equimolar doses of mannitol and 7.45% hypertonic NaCl solution (255 mOsmol each) were compared [154]. Here, mannitol as well as the hypertonic NaCl solution reduced elevated ICP (>20 mmHg) likewise; CPP was significantly increased in the mannitol group due to an increase in MABP.

The importance and position of osmotherapy in the cascade of different therapeutic interventions aimed at decreasing elevated ICP must still be defined. To date, SVR is discussed as a last possibility following unsuccessful administration of mannitol and barbiturates.

The search for the ideal osmotherapeutic continues. Overall, crystalloids [155] and mixed crystalloid/colloid solutions [156] appear to reduce ICP more efficiently than mannitol.

According to the equation developed by Frank Starling describing the intravasal colloid osmotic pressure required to balance the hydrostatic pressure gradient and to reduce development of extravasal edema formation which exceeds lymphatic drainage, it appears useful to maintain plasma albumin levels above 20 g/dL. Albumin substitution is indicated whenever plasma albumin is reduced in critically ill patients. The important role of albumin in the context of reducing brain edema formation is emphasized within the “Lund-concept” [157] (see Sect. 2.5.12.2). In a prospective randomized trial it was shown that administration of albumin 4% increased mortality compared to infusion of NaCl [158]. This increased mortality was caused by an excessive administration of albumin irrespective of plasma albumin concentrations.

2.5.11.1 Crucial Points and Pearls

- Reduction of brain edema can be achieved by infusing osmotically active solutions.
- Rare incidence of side effects, e.g., osmotic diuresis, electrolyte disturbances, osmotic nephropathy, rebound increases in ICP, must be considered.
- Detailed information, i.e., patients, time point, dose, and duration, must be identified to reduce the risk of secondary damage and increase the benefit of osmotherapy.

2.5.12 Controversial Issues Regarding Treatment Concepts: ROSNER vs. LUND

Following severe TBI prevention and reduction of cerebral ischemia is an integral part of modern intensive care treatment. Consequently, cerebral perfusion must be optimized to avoid functional and structural cell damage and to attenuate an increase in mortality and worsened outcome. However, it is difficult to define and assess an optimal cerebral perfusion at the bedside since regional and temporal heterogeneous changes in perfusion ranging from impaired perfusion due to local thrombus formation, tissue compression, and vasoconstriction to vasospasm as well as hyperemia are known to develop with individual profiles. Thus, we must rely on direct and indirect methods which we can use at the bedside to continuously assess pathologic changes and control effects of therapeutic interventions. New data support the concept of individualizing the different treatment options [159].

With the aim of improving cerebral perfusion and thereby protecting the brain two different concepts have been developed: the more senior “Rosner concept” and the younger “Lund concept.”

2.5.12.1 Rosner Concept

As described in the original work published by Rosner and colleagues in 1995 [160] CPP was maintained above 70 mmHg. For this, the patients received catecholamines, crystalloid (NaCl, Ringer Lactate), and colloid (albumin, mannitol) solutions and red blood cells (hemoglobin target > 12 g/dL) with the aim of

attaining a normovolemic state. CPP was also strongly influenced by the concomitant routine CSF drainage via EVD. Hyperventilation was not controlled. Patients were not given any barbiturates and hypothermia was not induced. Analgesia and sedation were not prioritized. The authors mainly focused on ICP-decreasing measures by CSF drainage and infusing mannitol and albumin. According to the original data, CPP was the main determinant to reduce ICP, suggesting a maintained cerebral autoregulation since an increased CPP will only reduce ICP if the cerebral vessels can respond to this increase in arterial pressure by vasoconstriction, thereby reducing intracranial blood volume. While lowest ICP was measured at a CPP of 123 mmHg in patients not requiring catecholamines, lowest ICP was recorded at a CPP of 90 mmHg in patients in need of catecholamines. Increasing CPP above 113 mmHg resulted in a nonsignificant trend towards elevated ICP. These data clearly demonstrate heterogeneity of functional responses in these patients and consequently question the contemporary opinion of categorically decreasing CPP to 60 mmHg. On average, patients requiring catecholamines had a higher ICP, i.e., 30.4 ± 14.7 vs. 18.1 ± 6.4 mmHg, were more severely injured, and exhibited an increased mortality. Overall mortality was 29%.

Retrospective evaluation of this large patient series does not allow to clearly identify individual treatment requirements since not all patients were treated identically: not all patients received mannitol, albumin, or catecholamines. A statistical subgroup analysis was not performed. In addition, these data were not compared to a historic or subsequently investigated group of patients. Consequently, the drawn conclusions are more suggestions than guidelines. It is important to acknowledge that the “Rosner concept” is not used in its original form and that it has been subject to various modifications, which have also not been investigated in appropriate studies. Nonetheless, it remains unchanged that we have to actively search for those phases in which CPP must be increased. Due to pathophysiologic changes which can occur rapidly and are difficult to predict, a rigid CPP value cannot be recommended as suggested in the current guidelines since impaired perfusion and hyperemia require different CPP targets. Already in their original work Rosner and colleagues clearly concluded that the search for an optimal CPP is dynamic and that the ideal CPP must be viewed in the context of cerebral changes over time. Contrary to the contemporary and insufficiently

documented official recommendation of categorically maintaining CPP around 60 mmHg Rosner and coworkers reported optimal CPP values between 85 and 90 mmHg. Experimental [161] and clinical data [162] show that reducing CPP increases structural damage and impairs cerebral oxygenation. Thus, the oversimplified concept of using a categorically defined CPP value must be considered outdated and wrong. Identification of an optimal CPP is only possible if specific monitoring methods, e.g., cerebral microdialysis, ptiO_2 and SjvO_2 measurement, local cerebral blood flow assessment using specialized probes [163], and TCD, are integrated in the clinical routine.

2.5.12.2 Lund Concept

The concept which was developed in Lund, Sweden, by pharmacologists, physiologists, and neurosurgeons focuses on pharmacologic modulation of cerebral and systemic targets by which the cerebral ischemic/hypoxic threshold is increased by the employed analgesia/sedation and by which the hydrostatic pressure known to aggravate brain edema formation is reduced [164]. The combination of these central targets allows controlled reduction of CPP. Reduction to low CPP values of 50 mmHg depends on metabolic monitoring of the injured brain using continuous microdialysis. Without metabolic monitoring there is an increased risk of missing pathophysiologic important changes, possibly resulting in secondary brain damage. Thus, metabolic monitoring via microdialysis allows to fine-tune the CPP level and adapt various therapeutic interventions, thereby reducing the risk of damaging potential of excessive therapeutic corrections. It is of high importance not to implement the “Lund concept” within the initial 24 h since any form of hypovolemia and possible coagulopathy must be corrected first.

The therapeutic aims are an ICP < 20 mmHg and a CPP between 50 and 60 mmHg, a SjvO_2 60–70% with an AJVDO_2 of 5–6 mL O_2/dL , a serum albumin of 40 g/dL, a hemoglobin between 10 and 13 g/dL, and a daily volume balance of 500 mL. In this context, CPP is not maintained at a rigid and categoric level of 50–60 mmHg, as generally misunderstood. Whenever signs of metabolic impairment unmask potential cerebral ischemia, CPP is increased until the underlying metabolic deterioration has been corrected. Only then can CPP be reduced again.

To achieve these goals cerebral as well as systemic targets are addressed. With the differentiated pharmacologic therapy different receptor subgroups are specifically inhibited or activated as patients receive fentanyl, midazolam, thiopental, or propofol. In addition, metoprolol and clonidine have a cardiodepressive as well as sedative effect. To reduce the hydrostatic pressure with the aim of decreasing the progression of vasogenic edema formation patients receive albumin, red blood cells, and fresh frozen plasma, thereby normalizing blood oncotic pressure. Concomitantly, patients receive a diuretic (furosemid) to promote diuresis and reduce hydrostatic pressure.

Those 53 patients who were investigated in the non-randomized and uncontrolled original publication showed an otherwise therapy-refractory ICP > 25 mmHg. Thus, these patients do not represent the general TBI population and the success was only compared to a historic group of patients. Consequently, the “Lund concept” cannot be generalized.

Based on heterogeneous lesions and the temporal as well as regional inhomogeneous changes interventions must be considered as being far more dynamic than currently acknowledged.

In principal, it is conceivable that patients could profit more from a fusion of the “Rosner concept” and the “Lund concept” – at least in some parts – than from strictly following rigid predefined values. An individual adaptation of the type and extent of therapeutic intervention, however, is only possible if correct monitoring methods are adequately integrated in daily routine.

2.5.12.3 Crucial Points and Pearls

- Neither the “Rosner concept” nor the “Lund concept” have been validated in prospective randomized clinical trials.
- Both concepts and at least individual parts of these concepts are justified in clinical routine. Criteria to determine which patients profit from which concept must be identified.
- Both concepts are not to be misunderstood as rigid concepts. Signs of deterioration require an adequate adaptation of the induced therapeutic interventions.
- Controlled reduction in CPP to low values of approximately 50 mmHg should only be performed with adequate neuromonitoring including cerebral microdialysis. At present, this is only possible in large centers.

2.5.13 Intraabdominal Compartment

In the past years the abdominal compartment has received increasing attention. Due to impaired gastrointestinal function resulting from hypervolemia-induced edema formation in conjunction with drug-induced gastrointestinal paralysis, the following pathologic changes must be anticipated:

- Increased ICP resulting from reduced venous drainage
- Bacterial translocation with subsequent sepsis
- Pulmonal deterioration with impaired oxygenation and ventilation

These changes, in turn, induce alterations which again activate systemic as well as cerebral destructive cascades, thereby contributing to and inducing secondary brain damage.

In this context, posttraumatic intraabdominal hypertension can increase ICP and reduce CPP, which is detrimental in patients with an impaired intracranial compliance and subsequent elevated ICP [165]. Surgical decompression of an abdominal compartment syndrome [166] can reduce ICP and mortality [167]. To prevent the development of an abdominal compartment syndrome it is important to guarantee regular bowel movements and to avoid hypervolemia.

2.5.13.1 Crucial Points and Pearls

- The abdominal compartment syndrome is also observed in patients with isolated severe TBI and influences the subsequent clinical course.
- Apart from intraabdominal injuries generalized edema can induce an abdominal compartment syndrome.
- Secondary problems are translocation of bacteria as well as impaired oxygenation and ventilation, which, in turn, activate destructive cascades and thereby induce secondary brain damage.
- Sometimes laparotomy must be performed to decrease otherwise therapy-refractory elevated ICP.

2.5.14 Drainage of Cerebrospinal Fluid

According to the Monroe–Kelly doctrine draining of CSF can reduce intracranial volume, thereby decreasing

ICP and supporting tissue viability by improving cerebral perfusion and oxygenation. This, however, requires an accessible ventricular system allowing to adequately position the catheter without injuring important structures such as the internal capsule and basal ganglia, and penetrating the floor of the third ventricle which could result in injury to the basal artery. Inserting a lumbar drainage also allows decreasing elevated ICP [168], which is only possible if patients are not at risk of cerebellar herniation. For this, basal cisterns and the foramen magnum must be clearly visible on routine CT scan.

While CSF drainage is generally recommended since it can positively influence the intracranial volume–pressure relationship there is no clear evidence regarding its general benefit. Proof of its benefit is hampered by the facts that a ventricular drainage can only be inserted in a small group of patients and that progressive brain edema and compression of the ventricular system preclude required CSF drainage. In principal, patients with severe TBI are not at increased risk of developing a hydrocephalus resulting from intraventricular hemorrhage with subsequent congested choroid plexus as found following ruptured aneurysm and spontaneous intracerebral hemorrhage. Thus, there is no forced necessity. Furthermore, repetitive or continuous CSF drainage can result in increased CSF production by the otherwise intact choroid plexus, which, over time, can also contribute to elevated ICP.

Penetration of the ventricular system and the duration of the CSF drain are associated with an increased risk for infections (ventriculitis and meningitis) irrespective of antimicrobial prophylaxis. The different risk factors, e.g., duration, frequency of drainage, type of catheter (i.e., with vs. without antimicrobial sheath), are discussed controversially [169]. Thus, a risk–benefit balance is indispensable to avoid inducing secondary brain damage.

2.5.14.1 Crucial Points and Pearls

- When properly indicated CSF drainage (ventricular or lumbar) can reduce elevated ICP.
- CSF drainage is not indicated in all patients and can only be performed properly in a subset of patients.
- A risk–benefit balance must be evaluated daily since a CSF drain is associated with serious complications such as hemorrhage, structural damage, and infections.

2.5.15 Craniectomy

Surgical treatment of otherwise therapy-refractory intracranial hypertension (>30 mmHg) includes uni- or bilateral decompressive craniectomy. In conjunction with an artificial expansion of the dura the intracranial space is increased, thereby significantly decreasing ICP and improving cerebral perfusion and oxygenation. In addition, therapy intensity can be reduced significantly [170]. However, disturbed autoregulation with an excessive increase in intracranial blood volume has been described following craniectomy [170]. To date, it remains unclear if decompressive craniectomy which is life saving and which facilitates a very good neuropsychological recovery [171, 172] should be performed preemptively in all patients. Whenever a craniectomy is indicated it is important to perform a sufficiently large craniectomy with concomitant expansion of the dura to avoid cerebral herniation with consecutive infarction at the edge of the exposed skull bone. Rigidity of the dura can cause an increase in ICP despite a large craniectomy.

2.5.15.1 Crucial Points and Pearls

- Otherwise therapy-refractory increases in ICP with signs of cerebral and cerebellar herniation are clear indications for uni- or bilateral craniectomy with concomitant expansion of the dura.
- Mortality and morbidity can be reduced.
- The indication of a preemptive craniectomy is currently unclear.

2.5.16 Corticosteroids

Since its identification as a significant inhibitor of phospholipase A_2 and blocking of subsequent activation of destructive prostaglandins and leukotrienes the same anti-edematous effect was searched following TBI as encountered in peri-tumorous vasogenic edema. This, however, was excluded in the study published by Gaab and colleagues in 1994 investigating the effects of high-dose dexamethasone [173] and confirmed in a recently published international multicenter double-blind placebo-controlled trial [174]. In this study, a total of 10,008 patients with mild to severe TBI were

randomized in two groups comparing the effects of methylprednisolone (2 g during the first hour, followed by continuous infusion of 0.4 g/h for 48 h) versus placebo. The aim was to determine a potential prophylactic effect of this glucocorticoid with mineralocorticoid action. Due to the significantly increased mortality during the first 2 weeks this trial was terminated prematurely. In addition, there was a trend towards an increased frequency of complications such as seizures, gastrointestinal hemorrhages, wound infections, and pneumonia in the steroid-receiving patients. These complications result from the well-described side effects of high-dose steroid administration: insulin resistance, increased energy consumption with hormonal, inflammatory, and immunologic dysfunction, muscular dysfunction, electrolyte imbalance, disturbance of the hypothalamic–pituitary–adrenal axis, reduced glucose uptake, and decreased cytoprotection. Consequently, based on international consensus prophylactic administration of steroids following TBI is obsolete.

To date, it is unclear if these constraints are also valid for hydrocortison, which is administered in a significantly lower dose to treat septic hypotension and adrenal insufficiency requiring increased administration of vasopressors and volume.

According to recent publications 20–50% of patients with severe TBI show signs of adrenal insufficiency of various degrees [175, 176] which require transient corrective administration of steroids. Apart from the primary brain damage secondary damage as well as pharmacologic side effects of different anesthetic and sedative agents (e.g., etomidate) are discussed as potential triggers [177]. Pituitary and hypothalamic disturbances with subsequent insufficient release of adreno-corticotrophic hormone (ACTH) or corticotropin-releasing hormone (CRH) result in insufficient stimulation of adrenal steroid synthesis. Clinically, cortisol deficiency presents with spontaneous hypoglycemia and arterial hypotension with increased catecholamine and volume requirement. In the adrenal cortex the mineralocorticoid aldosterone is also produced which is subject to a different regulatory hormonal circuit (renin–angiotensin–aldosterone system) and which can contribute to hypovolemia, hyponatremia, and hyperkalemia resulting from impaired synthesis.

Depending on the clinical situation these endocrinologic disturbances can be corrected by supporting systemic measures and specific administration of glucocorticoids and mineralocorticoids.

2.5.16.1 Crucial Points and Pearls

- Categorical administration of high-dose steroids following severe TBI is obsolete.
- Administration of low-dose steroids with mineralocorticoid effects can be indicated in patients with clinical signs of adrenal insufficiency (increased catecholamine requirement, hypovolemia, hyponatremia, hyperkalemia, hypoglycemia).

2.5.17 Prophylactic Antiepileptic Therapy

Following severe TBI the threshold for epileptic discharges is significantly decreased by the underlying structural and functional injuries which can trigger seizures at the time of injury, during the first week, and at later time points. In this context, free oxygen radicals which stem from the iron-containing hemoglobin found in hemorrhages are pathophysiologically important mediators that disturb glutamate uptake and different glutamate transporters [178]. This, in turn, aggravates glutamate-mediated excitotoxicity. Analog to animal experiments posttraumatic loss of hippocampal neurons has also been reported in humans and is thought to cause epileptic discharges [179]. In addition, a genetic predisposition in patients expressing the apolipoprotein $\epsilon 4$ allele is discussed [180]. Frequency of posttraumatic seizures is approximately 20–25%. Early after TBI, i.e., within the first 7 posttraumatic days, clinical as well as electrophysiologic signs of epileptic discharges are present [181]. In this context, nonconvulsive discharges and a nonconvulsive status epilepticus must be actively searched [182]. Seizures observed during the early phase appear to be triggered by acute intracerebral and intracranial hemorrhages, especially subdural hematoma, severe injuries, and chronic alcohol intake. Significant risk factors for seizures after the first posttraumatic week are seizures during the first week, intracranial hemorrhages, bitemporal contusions and multiple contusions, age > 65 years, midline shift > 5 mm, open TBI with bone displacement, impaired temporal perfusion, and hydrocephalus [183–185]. Late seizures have also been observed in patients with an initial Glasgow Coma Scale (GCS) 13–15, with the majority of patients exhibiting a GCS < 12 [184]. Long-term seizure activity results from hippocampal sclerosis, excessive neuronal excitation within the dentate gyrus, and uncoordinated neuronal

reorganization [186]. These morphological and functional alterations can result in therapy-refractory epilepsy and may even require surgical hippocampectomy [187]. Luckily, these structural and functional changes are not associated with cognitive deficits [185].

As a prophylaxis of possible epileptic discharges, official guidelines suggest administration of phenytoin for the first week which, however, did not prevent the development of seizures at later time points [188]. Whether administration of phenytoin will actually prevent early discharges during the first week is discussed controversially. According to Vespa and colleagues convulsive as well as nonconvulsive discharges could not be prevented by the early administration of phenytoin [182]. Thus, other reasons appear to be important. In this context, type and depth of sedation appears essential. It is conceivable that insufficient analgesia and sedation can promote seizure activity related to alcohol- and drug-related withdrawal after TBI.

Apart from phenytoin other drugs were evaluated, e.g., valproic acid, carbamazepine, barbiturates, levetiracetam [189], which, however, were not superior to phenytoin. In fact, levetiracetam was even associated with an increase in epileptic discharges observed in EEG analysis [190].

Overall, categorical administration of phenytoin with its also serious side effects and narrow therapeutic range must be viewed critically. In this context, phenytoin by itself can induce neuropsychologic impairment and can even induce arterial hypotension and cardiac arrest upon intravenous injection. Co-administration of various antibiotics can inhibit the cytochrome P450 system (CYP 3A4), thereby increasing phenytoin plasma levels, which, in turn, aggravates intended action but also its side effects.

Epileptic discharges must be actively searched for in sedated patients using EEG analysis. Ideal continuous EEG recording, however, requires extensive technical and personal support. Upon identification of typical epileptic discharges administration of antiepileptic drugs is justified. In awake and neuropsychologically adequate patients clinical observation without prophylaxis is possible and acceptable. To date, it remains unclear if these patients really profit from antiepileptic prophylaxis.

2.5.17.1 Crucial Points and Pearls

- Categorical and prophylactic administration of antiepileptic drugs is discussed controversially.
- Potentially damaging side effects must be balanced against unclear benefit.
- Available data do not allow to clearly assess different needs in antiepileptic prophylaxis in sedated and awake patients with significant structural damage.
- To date, a general and valid recommendation cannot be given.

2.6 Treatment Steps

To date, escalation of the different treatment modalities was based on absolute ICP values. Retrospectively, ICP was misinterpreted due to insufficient monitoring and ignorance of important and treatable problems in intensive care. In addition, official guidelines were phrased only for a few specialized centers. These guidelines which suggest starting treatment escalation only at an ICP 20 mmHg implicate a widely encountered fallacy that pathologic intracerebral processes do not exist at ICP values <20 mmHg. According to new experimental and clinical data pathologic changes do occur at ICP values <15 mmHg [22]. Furthermore, data are accumulating which clearly show that pathologic changes do occur despite adherence to the official guidelines [191]. This is best explained by the fact that modern intensive care treatment does not exist of categorical and static concepts as implied by the official guidelines. Pathologic changes characterized by their individual dynamic must be searched for actively. For this, adequate monitoring tools must be used and the search for novel diagnostic methods must continue. It is essential to understand that ICP and CPP – as suggested by the official guidelines – are insufficient when interpreted individually and must be complemented by additional monitoring methods. Furthermore, these patients should be treated in specialized centers with specially trained personnel, sufficient experience, and different monitoring techniques. In this context, mortality can be significantly reduced by experienced teams provided these hospitals treat more than 30 patients annually [82].

The following is an attempt to consider the multifaceted and dynamic changes in face of the official guidelines and contemporary knowledge and experience.

2.6.1 Crucial Points and Pearls

- Categorical treatment is not up to date and must be considered dangerous as it is too rigid and excludes flexible adjustments.
- Starting therapeutic interventions at an ICP > 20 mmHg is too late since many pathologic cascades are active at normal ICP levels (<15 mmHg).
- Only centers with sufficient expertise in surgery, anesthesiology, radiology, and intensive care medicine should treat patients with severe TBI.

2.6.2 Controlled Escalation

2.6.2.1 Basic Measures

The extent of the tiered treatment escalation as suggested in the official guidelines strongly depends on the type and extent of the chosen basic measures (Fig. 2.20). These basic measures, in turn, show large variance between different centers and strongly depend on knowledge, vigilance, attitude, and conviction of the treating physicians and nursing staff [192–194].

Basic measures consist of

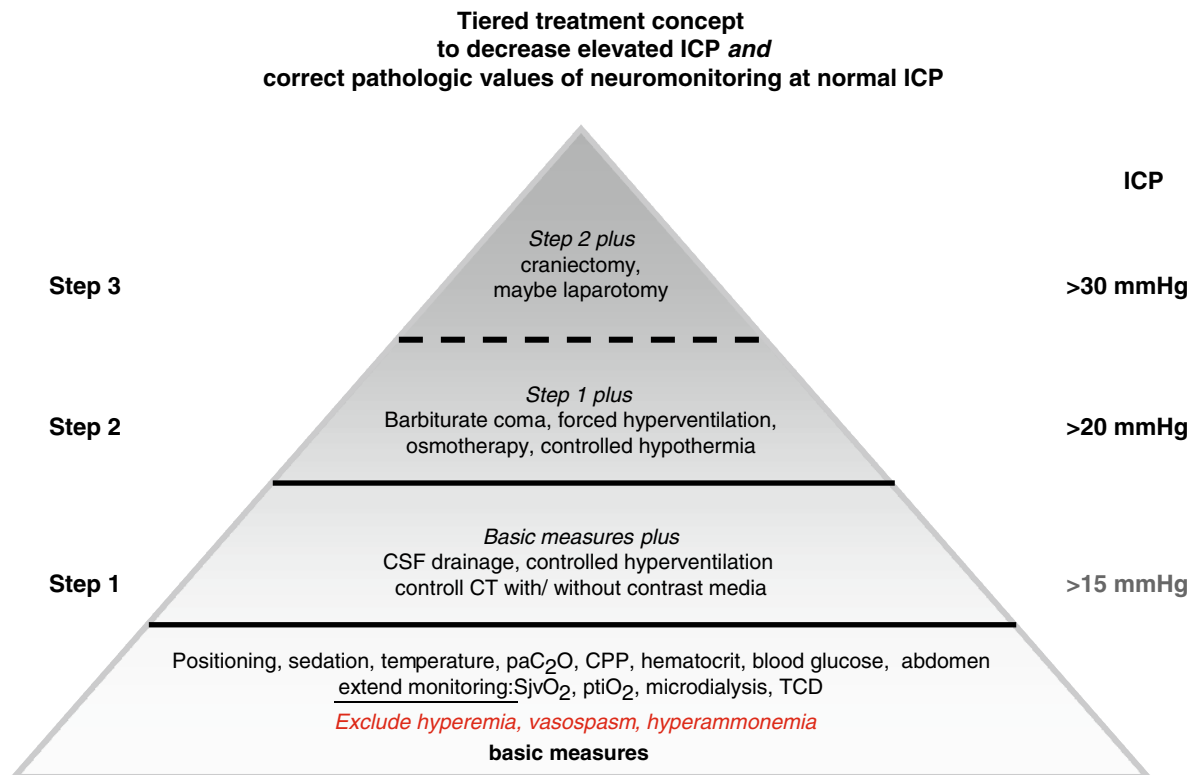


Fig. 2.20 Schematic drawing of tiered treatment consisting of different steps which are strongly influenced by the level of intracranial pressure (ICP). Contrary to the official guidelines which propagate to start escalating treatment at an ICP exceeding 20 mmHg we already search for possibilities to improve therapy as soon as we unmask pathologic alterations (“Stover concept”). These interventions are induced even at an ICP < 15 mmHg, if required, to correct pathologic findings. In this context, we predominantly see pathologically reduced jugular venous oxygen saturation (SjvO₂) values in face of elevated bispectral index (BIS) values in the first hours after trauma. This

pattern reflects insufficient analgesia and sedation but also prompts the search for impaired perfusion, hypotension, hypoxia, hyperventilation, anemia, fever, and seizure activity. Transient administration of thiopental (200–400 mg/h for 2–6 h) corrects signs of increased cerebral metabolism. Early and specific interventions require adequate monitoring and aggressive vigilance. Integrating the transcranial Doppler to unmask hyperemia or vasospasm guides specific interventions and allows to reduce unnecessary CT scans, especially in case of hyperemia since hyperemia-induced increases in ICP are caused by cerebral vasodilation

- Search for optimal positioning for an improved cerebral venous outflow
- Controlled analgesia and sedation, e.g., BIS EEG 20–40
- Temperature control (35–37°C) and pharmacologic/physical correction of fever
- Volume-controlled ventilation with normoventilation (paCO₂ 35–45 mmHg) considering ventilator-induced pulmonary changes (e.g., peak pressure < 35 mbar)
- Sufficient oxygenation, preventing hyperoxygenation (paO₂ > 11–13 kPa)
- Correcting anemia with increasing hematocrit > 28%
- Correcting hypo- and hyperglycemia
- Optimizing CPP through controlled administration of volume and catecholamines (without brain ischemia: 60–70 mmHg, with cerebral ischemia: 70–90 mmHg)
- Active search for hyperemia and vasospasms
- Regular control of blood ammonia levels

The intensive care phase is characterized by different phases in which ICP can remain above 20 mmHg despite maximal exhaustion of all treatment steps. In this context, it is indispensable to consider other important parameters to define the pathologic meaning of the actual ICP value, i.e., an ICP of 20 mmHg is acceptable as long as all other parameters reveal normal values. As long as these parameters, e.g., CPP, ptiO₂, SjvO₂, microdialysis, TCD, do not reveal any deterioration, controlled de-escalation within and between the different steps can be attempted.

2.6.2.2 Step 1

Whenever ICP > 20 mmHg (actual guidelines) (>15 mmHg at the University Hospital Zürich) a CT is performed to exclude a surgically removable hemorrhage (1) if the reason for this increase in ICP is not obvious at the bedside, and (2) if basic measures (Table 2.10, Fig. 2.20) fail to reduce elevated ICP within 20 min to < 20 mmHg (or <15 mmHg). In this context, it is important to be generous with CT scans since the majority of rebleeding and progression of hemorrhages occur early after TBI. At later time points, especially at the transition of the first to the second week of progression in brain edema, signs of vascular dysfunction (disturbed autoregulation, hyperemia) predominate. In the presence of functional pathologic alterations which cannot be corrected by optimized

treatment options a CT should also be performed at normal ICP values since patients with skull base fractures and resulting uncontrolled CSF leakage as well as patients previously craniectomized and those with inadequately inserted ICP probes and infratentorial pathologies are at an increased risk of missing otherwise elevated and pathologic ICP values. Extended neuromonitoring is indicated to define pathogenicity of the actual ICP and to guide subsequent interventions.

In case an EVD is used CSF drainage can be tried to decrease elevated ICP. Controlled hyperventilation (paCO₂ 35–45 mmHg) and osmotherapy can also be tried. Depending on the temperature moderate hypothermia (35°C) can be aimed for.

2.6.2.3 Step 2

With progressively increasing ICP > 25 mmHg or proven pathogenicity of any actual ICP even at lower ICP values (≤20 mmHg) controlled hyperventilation (paCO₂ >25 and <35 mmHg), barbiturate coma, and increased hypothermia (33–34°C) may be indicated.

2.6.2.4 Step 3

In case of therapy-refractory elevations in ICP (>30 mmHg) uni- or bilateral craniectomy and even laparotomy might be required. In this context, the transition between steps 2 and 3 is fluent.

2.6.2.5 Crucial Points and Pearls

- To guide type and extent of therapeutic interventions monitoring is indispensable.
- Treatment must not be based on ICP or CPP alone.
- A holistic, i.e., brain-oriented, therapy is superior to a brain-centered therapy to avoid inducing organ damage and not to confound anticipated neuroprotection by the induced organ damage.
- Therapeutic interventions should be based on tiered procedures; these tiered procedures, in turn, strongly depend on knowledge, vigilance, attitude, and conviction of the involved team members.
- Without specific knowledge of local and systemic secondary insults senseful therapy of patients with severe TBI is not possible.

Table 2.10 Possible reasons for elevated intracranial pressure (ICP) and potential therapeutic measures

Reasons for increase in ICP	Diagnostics	Possible therapy
<i>Local</i>		
Space occupying lesion: hemorrhage, edema	CT	Surgery: evacuation, craniectomy Pharmacology: barbiturate coma, osmotherapy, hypothermia
Vasodilation, hyperemia	TCD, ptiO ₂ , SjvO ₂ , hematocrit	Controlled hyperventilation, controlled reduction of CPP < 70 mmHg, transfusion
Vasospasm	TCD, imaging (e.g., CT with contrast agent), microdialysis, ptiO ₂ , SjvO ₂	Controlled hypoventilation, controlled increase of CPP to 110 mmHg
Disturbed autoregulation	ICP curve analysis, PC-guided analysis	Controlled adaption of CPP, slow rewarming
Ischemia	TCD, microdialysis, ptiO ₂ , SjvO ₂	Controlled hypoventilation, controlled increase of CPP
Insufficient analgesia/sedation	Clinical picture (straining, coughing, hypertension), BIS EEG, SjvO ₂ , ptiO ₂ , microdialysis	Increase dose of analgetics/sedatives, switch to or add more potent drugs
Epileptic discharges	Clinical picture (convulsions), EEG (active search for status epilepticus nonconvulsive), microdialysis, ptiO ₂ , SjvO ₂	Antiepileptic drugs
Cortical spreading depression	Special electrodes	Increase blood glucose levels (> 5 <10 mM), barbiturate coma, hypothermia
Sinus thrombosis	CT with contrast agent	High dose heparin, barbiturate coma and hypothermia with hemispheric edema
<i>Systemic</i>		
Arterial hypotension	Temperature, blood pressure amplitude, hematocrit/coagulation including factor XIII), electrolytes, sonography/CT Abdomen; Picco® catheter, pulmonary artery catheter Exclusion: Infection/sepsis Adrenal insufficiency	Reduce fever or slow down rewarming, administer volume, correct possible bleeding, treat infection/sepsis, consider glucocorticoids/mineralocorticoids
Intraabdominal hypertension, paralytic ileus, abdominal compartment syndrome	Clinical picture (abdominal pressure, peristaltic sounds, pulmonary function, pulmonary pressure, diuresis), bladder pressure	Aggressive mechanical and pharmacological stimulation, consider laparotomy Change enteral nutrition solution Reduce volume administration
Arterial hypertension	Withdrawal symptom with tachycardia, mydriasis, sweating, diarrhea; Herniation sign with bradycardia Excessive volume infusion	Increase analgesia/sedation Decrease arterial blood pressure; avoid nitrates due to cerebral vasodilation Withdrawal: clonidine plus propofol Administer diuretic ± albumin
Positioning	Clinical picture, change vertical and lateral position	Adapt vertical and lateral position
Hyperammonemia	Analyze blood ammonia level	Change nutrition, reduce protein load, stop antiepileptic drugs, start specific therapy/dialysis

2.6.3 Controlled De-escalation

While escalation of different therapeutic interventions was investigated and is considered in guidelines we are lacking detailed information regarding de-escalation cedures (100). In general, we can advise that de-escalation should be performed slowly and should also be subject to adequate control to avoid any overshooting and thus damaging reactions resulting from an abrupt stop of different interventions. In this context, abruptly stopping analgetics and sedatives will provoke withdrawal symptoms consisting of uncontrolled vegetative alterations, i.e., hyperventilation and hypertension, which, in turn, can induce secondary brain damage. This must be avoided implicitly. In addition, strong variations in blood pressure, CPP, blood glucose, and sodium must be avoided.

Apart from controlling escalation multimodal neuromonitoring allows guiding a controlled de-escalation. In this context, limits of paO_2 and paCO_2 , CPP, hematocrit, and blood glucose can be corrected dynamically to lower values, thereby reducing the extent of therapeutic interventions. Thus, these new limits are adapted to the actual situation with individual needs. In this context, continuously measured ptiO_2 allows to reduce paO_2 , decrease paCO_2 , and adapt CPP to low levels and also reduce hematocrit to, for example, 24% (Fig. 2.21). This, in turn, allows reducing the extent and aggressiveness of therapeutic interventions, thereby diminishing the risk of organ-damaging potential of a too aggressive ventilatory support and a too aggressive volume administration. In addition, transfusion requirement can be attenuated with a good conscience.

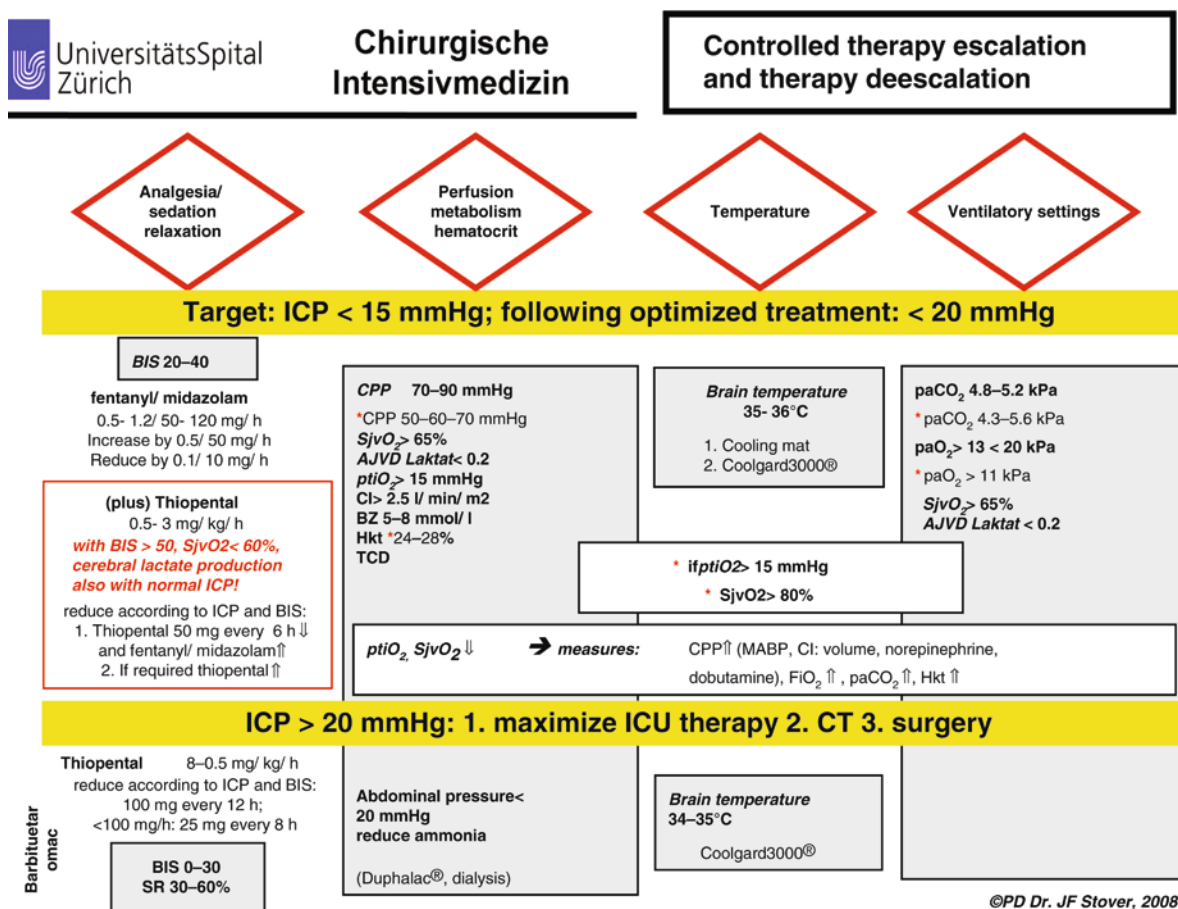


Fig. 2.21 Example of the tiered treatment paradigm involving different therapeutic interventions practiced at the University Hospital Zürich for a controlled escalation and controlled de-escalation (“Stover concept”). Depending on the clinical situation and the nature of the diagnosed pathological findings,

therapeutic interventions are adapted dynamically. For this, more than one intervention combined with escalation and de-escalation of different interventions might be required simultaneously

The wake-up period should also be controlled. Here it is essential to base all decisions on the presence of brain edema as seen in control CT scans. As long as signs of hemispheric edema are present analgesia and sedation should not be stopped. However, complete resolution of hemispheric edema does not guarantee a smooth wake-up phase. Even local brain edema can promote an increase in ICP in conjunction with disturbed cerebral autoregulation, which precludes reducing analgesia/sedation. Whenever signs of functional deterioration such as decreased $SjvO_2$ levels develop wake-up should be halted and even a new controlled escalation might become necessary to avoid secondary insults and induction of secondary brain damage. This, in turn, requires adequate monitoring during the vulnerable wake-up phase.

2.6.3.1 Crucial Points and Pearls

- Apart from controlling escalation of different therapeutic interventions, controlled de-escalation is also of imminent importance to avoid missing and actively inducing secondary insults and secondary brain damage.
- Controlled de-escalation requires multimodal monitoring, which allows adapting type and extent of different therapeutic interventions to prevent organ damage of a possibly excessive and overshooting treatment.
- During controlled de-escalation a new controlled escalation might become necessary to correct new pathologic alterations.
- Presence of hemispheric edema forbids wake-up trial.
- Absent signs of hemispheric edema does not guarantee unproblematic wake-up.

2.7 Difficult Decision Making

Contrary to patients with obvious pathologic CT scan and severe obvious neurologic deficits ($GCS < 9$) patients with an initially unremarkable CT scan with severe neurologic defects and those with a pathologic CT but only marginal or even absent neurologic deterioration ($GCS > 13$) are very difficult to predict in terms of subsequent deterioration, preemptive neuroprotection

including intubation, controlled ventilation and oxygenation, optimized CPP, analgesia/sedation, and control of ICP and $SjvO_2$. Without signs structural damage in the initial CT neurologic impairment observed at the site of injury can disappear completely or reflect the clinical equivalent of diffuse axonal injury which cannot be determined in the initial CT scan. Neglectful decision making would retrospectively prove wrong if diffuse axonal injury were diagnosed in the control CT scan or MRI. Neglectful decision making, in turn, would imply allowing secondary insults to occur. Patients with clearly pathologic CT findings and stable $GCS > 13$ would be treated falsely until the secondary neurologic deterioration reflects progression of the structural damage. Again, false decision making will only become obvious retrospectively. Whether this justifies preemptive intubation and positioning of an ICP probe will spur controversial discussions.

2.7.1 Initial GCS

The initial GCS tempts us to inadequately judge intracranial pathology if patients are evaluated too early, they are not recovered for a longer undefined period, they are hypothermic, they are under the influence of alcohol and drugs, they are multiply injured, or if they cannot be assessed adequately due to severe aggressive behavior. Indicated intubation with subsequent sedation renders a further sensible evaluation impossible. Furthermore, stress factor for those who determine the GCS at the site of injury must also be considered. A further misjudgment is given by the imbalance of the three parts of the GCS (eye opening, verbal communication, motor response). A low/bad GCS which is mainly influenced by the motor response must be weighted differently compared to a low GCS which is dictated by the results obtained for eye opening and verbal communication, especially if there is a language barrier or the patients are aphasic. Approximately 20% of all patients are judged to be too severely injured according to the GCS [195, 196]. Furthermore, clinical experience shows that the initial GCS is not a reliable prognostic factor. While mortality is significantly increased at $GCS < 8$ compared to a $GCS > 13$, an initial $GCS > 13$ does not guarantee survival in these patients. Up to 10% of patients with severe TBI succumb due to rapidly progressing intracranial pathologic alterations, which are also

influenced by age and further complications such as coagulopathy and severe infections with multiple organ failure. Early signs of beginning herniation are not equal to definite mortality [197].

At a GCS < 8 all therapeutic options should be considered and a definite decision should not be made since not all patients will die and a reluctant attitude might induce preventable secondary insults and thus convey secondary brain damage. At a GCS > 13 we are not allowed to grow negligent as this attitude might also allow many otherwise preventable secondary insults.

2.7.2 First CT Scan Following Severe Trauma and GCS

Depending on the duration between the accident and initial CT scan the resulting time span might be too short to clearly identify intracranial injuries. Hemorrhages, contusions, and edema require time to develop. Usually these lesions will reach their maximal extent during the first 24 h [198]. Unfortunately, in many patients neurologic evaluation insufficiently reflects evolving damage. Any form of neurological deterioration implies an immediate CT scan. Newly diagnosed lesions will then force new decisions. In this context, it is important to realize that GCS shows a strong variability depending on the underlying intracranial compliance which is strongly influenced by age and the corresponding degree of cerebral atrophy. GCS > 13 is not equivalent to small or absent lesions. GCS < 13 does not necessarily imply large lesions with midline shift, as diffuse axonal injuries might be present.

A patient with an initially low GCS > 9 who recover to a GCS of 11–13 must be evaluated neurologically every hour in the emergency room, ICU, and intermediate care, depending on the present infrastructure. When in doubt, repetitive CT scans are required, especially if the patient is under the influence of drugs and alcohol. Whenever, signs of progression and deterioration become evident the patient should be transferred to a specialized center.

Whenever patients remain neurologically stable for at least 24 h (initial GCS > 13) or even improve they can be transferred to a normal ward following control CT scan. With signs of midline shift and progressive brain edema patients should remain in the ICU for a further 24–48 h, even in case of GCS > 13.

Patients with pathologic CT findings and undulating vigilance (GCS 11–13) and even a GCS > 13 must be examined at short intervals and subjected to repetitive CT scans. It is important to actively search for vegetative changes such as tachypnea, hyperventilation, hypertension, and hypotension. Thus, these patients must be controlled on an ICU and require an arterial line to continuously measure mean arterial blood pressure (MABP) and control paCO_2 . Only then can we unmask and prevent secondary insults. To prevent hyperventilation-induced cerebral vasoconstriction patients with a GCS > 11 might even require preemptive intubation and insertion of an ICP probe. To date, it remains unclear if these patients (GCS > 9) would profit from preemptive intubation and controlled escalation for at least the first 24 h, which is regarded as the most vulnerable phase. Surely, some patients would be intubated in vain and would remain sedated for at least 24 h until the first control CT scan. This could be justified as our main emphasis is to prevent secondary brain damage to increase the regeneration potential of these patients.

In patients who present with an initially unremarkable CT scan following a high-velocity accident or fall (>2 m height) and who must be intubated for surgical stabilization of fractures and additional injuries resulting in impaired neurologic evaluation, a control CT scan should be performed within 6 h. This is indispensable whenever patients develop intraoperative complications including arterial hypotension and coagulopathy. This reduces the risk of missing relevant lesions which develop during the first hours and allows appropriate interventions including insertion of an ICP probe.

2.7.3 Time Point for Surgery

While surgical care of serious and potentially lethal thoracoabdominal and hemorrhagic injuries are treated according to the principle “treat first what kills first,” the situation with severe but not immediately life-threatening injuries is less clear and more difficult to evaluate. This mainly pertains to the surgical stabilization of pelvic and long bone fractures in the early phase. Early surgery of these fractures can result in a severe coagulopathy with hemorrhages and arterial hypotension which, in turn, induce autodestructive and

difficult-to-manage, and even lethal cascades. It is important to follow the “damage control” principle with initial external fixation since imaging cannot unmask the complete extent of injuries [199]. In this context, clinically based sepsis, which requires experience and differentiated knowledge, is of imminent

importance. Trauma mechanism and imagination of possible injuries and deteriorations developing within the first 24 h force us not to underestimate any injury [200]. Only then can we reduce the risk of secondary insults and an increase in secondary brain damage (Figs. 2.22 and 2.23).



Fig. 2.22 Clinical example of unexpected lesions which determined further clinical course in this patient. Following the crash of a Learjet during landing the patient suffered severe pelvic fractures, and distal fractures to the femur and tibia with a large occipital bleeding scalp lesion. Based on the initial Glasgow Coma Scale (GCS) score of 13 and the unremarkable cerebral computed tomography (CT) which was performed 2 h after trauma (**a**, **b**) unanimous decision was to operate the long bone fractures in this patient. During surgery the patient developed severe disseminated intravascular coagulopathy inducing anemia and arterial hypotension. Control CT scan performed 12 h after trauma (**c**, **d**) revealed large bifrontal space-occupying contusions, and contre-coup lesions to the severe bleeding occipital scalp lesion. In addition,

left hemispheric edema developed (effaced sulci and gyri) (**d**). Due to the persisting and difficult-to-correct coagulopathy and abdominal complications the patient succumbed 7 days after trauma. This case impressively and convincingly shows that following high-velocity injuries severe intracranial lesions must be anticipated. In addition, this case clearly demonstrates that CT scans which are performed “too” early cannot reveal cerebral lesions, which in some patients require time to develop. Thus, these patients would be subjected to an increased risk for secondary brain insults. Surgeries with increased risk for hemorrhages and sustained danger of arterial hypotension and coagulopathy should be postponed until after the control CT scan at 24 h, provided these surgeries are not life-saving

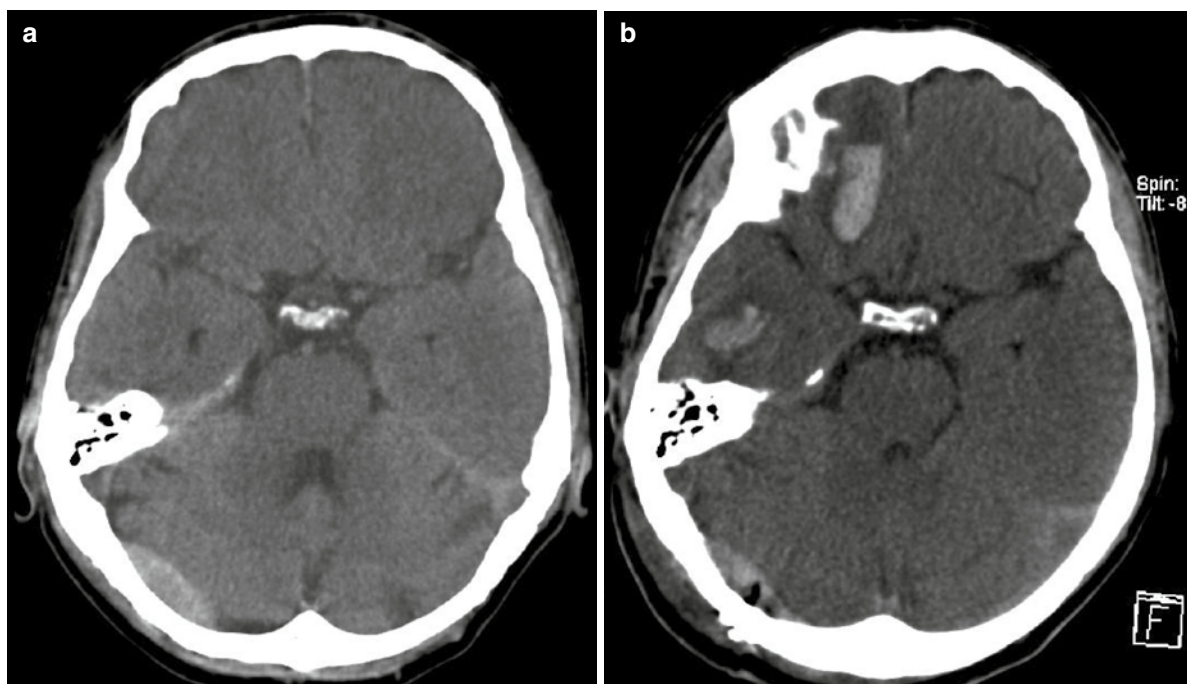


Fig. 2.23 Clinical example of unexpected contre-coup contusions following an initial isolated occipital infra- and supratentorial epidural hematoma (**a** and **b**). Following removal of the epidural hematoma the patient was extubated and constantly had

a GCS score of 15. In the CT scan routinely performed 24 h after trauma, frontal and temporal contusions were found (**b**). The epidural hematoma had continued bleeding without clinical relevance

2.7.3.1 Reconstruction of Midfacial Fractures

To optimize conditions for surgical repair of extensive midfacial fractures with and without skull base surgery MABP is reduced intraoperatively pharmacologically using clonidine and nitroglycerin to 60 mmHg with the aim of reducing hemorrhage in the surgically exposed area. Reducing MABP to such low values in combination with nitroglycerine-induced cerebral vasodilation can increase the risk for cerebral secondary brain damage with brain edema formation or aggravation of underlying brain edema. This risk persists for several weeks following severe TBI. It also appears that elevated vulnerability of the injured brain is still present weeks after TBI even after brain edema has resolved.

2.7.4 Influence of Different Factors on Morbidity and Mortality

To identify relevant factors determining subsequent development following severe TBI many clinical and demographic analyses as well as assessment of changes

in various parameters in blood and CSF including the individual genetic profile have been considered. These results were then evaluated in the context of mortality and morbidity. Taken together, the following factors were identified to significantly influence mortality and morbidity: age [201], female sex [202], initial GCS and pupil abnormalities [203], type and extent of intracranial damage including brain stem lesion and midline shift [204], presence of secondary insults [205], preexisting alcohol and drug addiction [206, 207], presence of pathologic lab values [110], confirmation of a specific genetic APO-E profile [208], elevated NSE [209], S-100 [210], GFAP [211], IL-10 [212], and troponin values [213].

The inherent problem of these determinant factors is the statistical analysis which allows a certain misinterpretation due to the used probability value ($p < 0.05$). A $p < 0.05$ corresponds to a probability of 5% of the investigated collective in which an identified parameter is not correctly allocated. This, in turn, means that at a $p < 0.05$ 5 of 100 (i.e., every 20th patient) are misinterpreted. These patients, however, cannot be identified properly. Consequently, none of these factors guarantee an absolute secure and valid

predictability. Thus, a generalization in patients without clear signs of brain death is impermissible and results in chaining of incorrect decisions, especially since all identified factors were assessed under the influence of ongoing surgical, anesthesiological, and intensive care interventions with possible complications [214] including inadequate nutrition [215] without having questioned these “basic” influences and without controlling for these influences. The identified factors imply that all therapeutic interventions are correct and that no secondary insults occurred.

These identified influencing factors can only be used to investigate whether adequate and aggressive diagnosis and therapy must be established early to support the regenerative potential in these patients. This, however, requires an adequate professional attitude and conviction as well as the ability to make decisions based on the sum of different parameters and complex interactions. Furthermore, an adequate infrastructure is indispensable to allow maintaining prolonged pharmacologic coma depending on the duration of persisting brain edema.

2.7.4.1 Crucial Points and Pearls

- The initial GCS is insufficient in predicting type and extent of intracranial damage and cannot forecast further development. At a GCS < 8 we are not allowed to give up and at a GCS > 13 we are not allowed to grow neglectful.
- The initial CT does not reveal the full extent of the lesions. According to the clinical picture, an early control CT scan must be performed, especially in intubated patients and those in whom intraoperative complications such as arterial hypotension, hemorrhage, and coagulopathy occurred.
- The initial stabilization of additional injuries must consider the existing leading injuries and possible complications such as hemorrhage and coagulopathy to avoid unnecessary endangerment of these patients. When in doubt, fractures should primarily be stabilized with external fixation and definite stabilization should be performed after control CT scan has excluded or at least unmasked brain lesions. Then, secondary brain damage can be prevented.
- Surgical reconstruction of complex facial fractures should not be performed as long as brain edema persists.
- Prognostic relevance of different factors for the individual patient appears to be of subordinate importance and should not be used to limit treatment prematurely but should rather promote search for optimized treatment.

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