

Fine tuning of neurointensive care in aneurysmal subarachnoid hemorrhage: From one-size-fits-all towards individualized care



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ABSTRACT

Aneurysmal subarachnoid hemorrhage (aSAH) is a severe type of acute brain injury with high mortality and burden of neurological sequelae. General management aims at early aneurysm occlusion to prevent re-bleeding, cerebrospinal fluid drainage in case of increased intracranial pressure and/or acute hydrocephalus, and cerebral blood flow augmentation in case of delayed ischemic neurological deficits. In addition, the brain is vulnerable to physiological insults in the acute phase and neurointensive care (NIC) is important to optimize the cerebral physiology to avoid secondary brain injury. NIC has led to significantly better neurological recovery following aSAH, but there is still great room for further improvements. First, current aSAH NIC management protocols are to some extent extrapolated from those in traumatic brain injury, notwithstanding important disease-specific differences. Second, the same NIC management protocols are applied to all aSAH patients, despite great patient heterogeneity. Third, the main variables of interest, intracranial pressure and cerebral perfusion pressure, may be too superficial to fully detect and treat several important pathomechanisms. Fourth, there is a lack of understanding not only regarding physiological, but also cellular and molecular pathomechanisms and there is a need to better monitor and treat these processes. This narrative review aims to discuss current state-of-the-art NIC of aSAH, knowledge gaps in the field, and future directions towards a more individualized care in the future.

1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a severe form of acute brain injury that is treated in the neurointensive care (NIC) unit. The mainstay of NIC is to monitor systemic and cerebral physiology and to prevent and treat avoidable factors that could otherwise induce secondary brain injury.^{1,2} Since the initiation and development of NIC, clinical outcome has significantly improved for aSAH patients.² However, several challenges still exist.

First, current aSAH guidelines^{3,4} and local management protocols⁵ of NIC variables such as intracranial pressure (ICP) and cerebral perfusion pressure (CPP) are either absent or to a great degree developed based on those from severe traumatic brain injury (TBI), which stands as the prototype disease in NIC. However, the same targets and thresholds may not apply in both diseases.⁶ Second, the same NIC targets are to a great extent applied for all aSAH patients under most circumstances, despite inter- (demography, co-morbidities, extent of injury) and intraindividual (throughout the temporal course of the acute phase) differences. Third, current NIC targets such as ICP and CPP are only surrogates of the cerebral environment, but their validity to predict the actual intracranial

state globally and focally may be questioned.^{7,8} The development of new multimodality monitoring (MMM) tools to assess cerebral blood flow (CBF; imaging and invasive probes), CBF autoregulation (e.g. pressure reactivity index), brain tissue oxygenation (btO₂ and jugular bulb), and cerebral energy metabolism (microdialysis) have improved our understanding of disease pathophysiology and the cerebral effects of treatments, but their validity to guide management still remains unclear considering their inherent temporal, spatial, and logistical constraints. Fourth, the focus of NIC has been directed towards systemic and cerebral physiological optimization, but this does not address all pathomechanisms that occur on a cellular and molecular level such as neuroinflammation, neurodegeneration, and neurorepair.^{9,10} A better understanding of this could potentially contribute to the development of appropriate pharmacological agents and administration of these in an optimal time window based on high-resolution bedside monitoring data.

Consequently, although the development of NIC in aSAH has been a success from a historical point of view,² there is clearly room for further improvement. The aim of this narrative review was to discuss the current knowledge gaps, the limitation of extrapolation of TBI guidelines to aSAH,^{3,4,11} and more particularly about fine tuning of NIC in aSAH to

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individualize care both in terms of cerebral physiology and molecular injury patterns.

2. Individualized therapy in neurointensive care – the role of multimodality monitoring

There are several physiological steps that affect CBF and the cerebral delivery of oxygen (CDO₂) as well as nutrients (glucose and lactate; CDGlc and CDLac) and there are many pathomechanisms that may interfere (Fig. 1). Evolving secondary brain injury can be fairly detected as a neurological deterioration, clinically assessed by repeated neurological examinations, although this is more challenging in unconscious patients that require intubation, mechanical ventilation, and sedation. In classic NIC, ICP and CPP are monitored in unconscious aSAH patients and treatment aims to avoid intracranial hypertension and to ensure sufficient cerebral perfusion. However, even in case of normal ICP and CPP, disturbances in CBF, btO₂, and cerebral energy metabolism are frequent.^{8,12–14} For that reason, there has been a development of MMM tools to enable monitoring of the different steps to achieve cerebral energy metabolism (Tables 1 and 2). Monitoring may then also include cerebral pressure autoregulation (pressure reactivity index, mean flow index), CBF (intraparenchymal probes, transcranial Doppler, and radiological imaging), brain tissue oxygenation (jugular bulb, btO₂), and cerebral energy metabolism (microdialysis and radiological imaging). Ideally, a complete MMM setup enables earlier detection of impending brain injury and diagnosis of the specific pathomechanisms, which in turn predispose for more cause-specific therapies. However, so far, the implementation of MMM-based management has been limited to a few research-oriented NIC units.^{15,16} A major reason for this is that controversy remains regarding the validity to guide management based on these MMM-tools. For example, the microdialysis only represents a small brain region and the rationale to guide a global therapy such as CPP-levels is questionable considering the regional differences in cerebral injury patterns and pathophysiology.⁷ At the same time, a global measure such as jugular bulb oxygenation may be too insensitive to detect small, but important, focal cerebral oxygen disturbances. Another problem is that some methods such as radiological imaging only gives snap-shots of the cerebral status. However, even if no MMM tool is perfect, the combined analysis of the information obtained by the different

techniques may provide a more accurate picture of the cerebral situation. Altogether, MMM carries great potential, despite existing limitations (Fig. 2). In the sections below, we discuss the different steps to optimize cerebral energy metabolism divided into the CBF-, oxygenation-, and nutrient-pathways together with factors involved in energy metabolism (Fig. 1).

3. Individualized therapy – physiological targets to optimize cerebral energy metabolism

3.1. Optimizing CBF

Fig. 1 describes the pathways to optimize cerebral energy metabolism. It is key to maintain a sufficiently high CBF to achieve adequate CDO₂ and CDGlc/CDLac. CBF disturbances are common in aSAH⁸ and may be attributed to several pathomechanisms, as discussed below.

3.1.1. ICP-monitoring, thresholds, and treatments

During ictus, there is a rapid increase in ICP following the hemorrhage from the ruptured intracranial aneurysm. Thereafter, secondary ICP elevations may occur in both an acute (<24 h) and delayed (2–14 days post-ictus) fashion due to e.g. re-bleeding, acute hydrocephalus, intracerebral hemorrhage, subdural hematomas, diffuse global cerebral edema, and cerebral edema.¹⁷ High ICP may in turn induce compression of neural structures as well as lead to macro- and microvascular CBF disturbances by lowering CPP and inducing capillary collapse.¹⁸

In an aSAH cohort study of patients with EVD-monitoring due to unconsciousness or hydrocephalus, ICP elevations were found to be very common. Around 80% of the patients exhibited at least one episode of ICP above 20 mmHg for more than 5 min.¹⁹ Still, the role of ICP monitoring, the definition of elevated ICP, and protocols for when ICP-lowering treatments are warranted remain controversial. Currently, the Neurocritical Care Society (NCC) has no recommendation on ICP-monitoring or ICP-lowering treatments,⁴ whereas the American Heart Association (AHA) suggests cerebrospinal fluid (CSF) drainage with an EVD or a lumbar drainage in case of acute hydrocephalus,³ but the role of ICP-monitoring, per se, and ICP-lowering treatments are not stated. Due to the lack of recommendations from aSAH guidelines, most centers, including ours, have extrapolated the ICP-regime from TBI protocols.^{5,11,20}

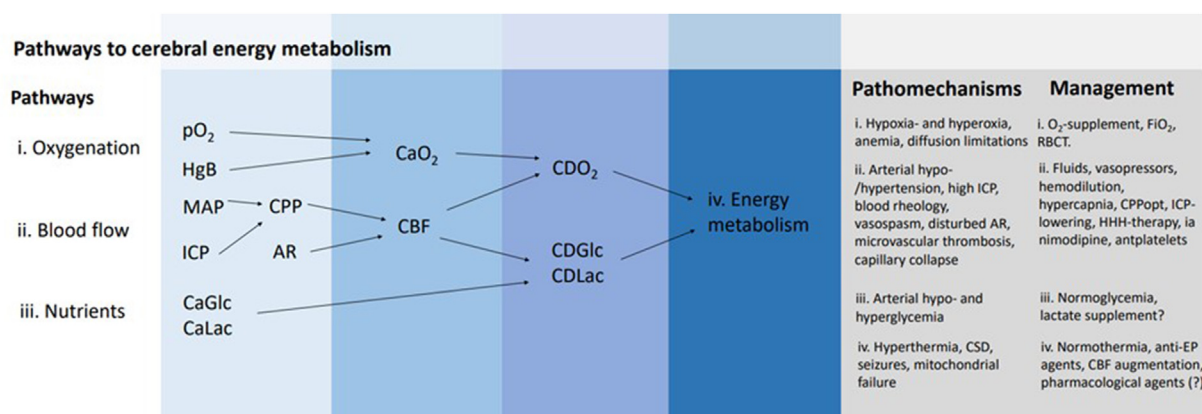


Fig. 1. Physiological pathways, pathomechanisms, and management options to optimize cerebral energy metabolism in aSAH.

The figure describes the different pathways to ensure cerebral energy metabolism. In the CBF pathway, MAP and ICP determine CPP, which together with the cerebral autoregulation determine CBF. In the oxygenation pathway, pO₂ and HgB determine the CaO₂, which together with CBF constitute the CDO₂. In the nutrient pathway, CaGlc and CaLac are defined as the arterial content of these metabolites, which together with CBF determine CDGlc and CDLac. CDGlc, CDLac, and CDO₂ are necessary for the cerebral production of energy, which takes place in the cytosol and mitochondria of the brain cells. Several pathomechanisms may interfere with each step, which can be addressed to some extent with specifically targeted management strategies, as suggested in the figure.

AR = Autoregulation, aSAH = Aneurysmal subarachnoid hemorrhage, CaGlc = Arterial content of glucose, CaLac = Arterial content of lactate, CaO₂ = Arterial content of oxygen, CBF = Cerebral blood flow, CDGlc = Cerebral delivery of glucose, CDLac = Cerebral delivery of lactate, CDO₂ = Cerebral delivery of oxygen, CSD = Cortical spreading depolarization, EP = Epilepsy, FiO₂ = Fraction of inspired oxygen, Hgb = Hemoglobin, HHH = Hemodilution, hypertension, and hypervolemia, ICP = Intracranial pressure, MAP = Mean arterial blood pressure, pO₂ = Partial pressure of oxygen, RBCT = Red blood cell transfusion.

Table 1
Multimodality monitoring – a selection of methods and their benefits and limitations.

| Physiological variable | Monitoring method | Advantage | Limitations |
|----------------------------|--|--|--|
| ICP | EVD | Both monitoring and treatment of ICP by CSF drainage. | Infections. Clotting of the EVD. |
| CPP | Intraparenchymal probe Any ICP monitor combined with arterial line for continuous systemic ABP. | Less invasive than EVD. Continuous global estimate of CBF. | Does not offer ICP treatment with CSF drainage. Zero-drift. Spatial constraints; does not take into account differences in cerebral autoregulation or vasospasm. |
| CBF autoregulation | PRx (ICP and ABP) | Measure of the global autoregulatory status. | Requires ICP-monitor. Low signal-to-noise ratio. Spatial constraints; insensitive to focal disturbances. |
| | CPPopt (PRx and CPP) | Global CBF surrogate that takes into account autoregulatory status. | Requires advanced software. Still insufficiently studied in aSAH. Spatial constraints; insensitive to focal disturbances. |
| | Mx (TCD and CPP) | Easy to use bedside. May detect regional autoregulatory differences. | User-dependent. Spatial constraints; limited global spatial validity, especially in the posterior circulation |
| Cerebral blood flow | Radiology (Perfusion-CT, Xe-CT, PET, MRI) | Both global and focal. | Logistics; Difficult to transport unstable patients to the radiology department. Time constraints; represents only a snapshot. |
| | TCD | Easy to use bedside. | Measures velocity, not CBF. User-dependent. Spatial constraints; limited global spatial validity, especially in the posterior circulation. Time constraints; monitoring occurs in a limited time interval. |
| | Intraparenchymal thermal diffusion probe | Continuous CBF measure. | Spatial constraints; limited global spatial validity. |
| Brain tissue oxygenation | Jugular bulb catheter (SjvO ₂) | Continuous and feasible global measure. | Spatial constraints; low sensitivity for focal ischemia. |
| | Intraparenchymal device (BtO ₂) | Continuous and feasible focal measure. | Spatial constraints; limited global spatial validity, especially in the posterior circulation |
| | NIRS | Non-invasive. | Spatial constraints; limited global spatial validity, especially in the posterior circulation |
| Cerebral energy metabolism | MD | Feasible for continuous evaluation. | Spatial constraints; limited global spatial validity. |
| | PET | Possible to investigate focal/global complex aspects of energy metabolism. | Logistics; Difficult to transport unstable patients to the radiology department. Time constraints; represents only a snapshot. |
| | EEG | Helpful to diagnose cerebral ischemia and NCSE | Complexity; difficult to interpret bedside. |

ABP = Arterial blood pressure, CBF = Cerebral blood flow, CSF = Cerebrospinal fluid, EEG = Electroencephalography, EVD = external ventricular drain, ICP = Intracranial pressure, MD = Microdialysis, Mx = Mean flow index, NCSE = Non-convulsive status epilepticus, NIRS = Near infrared spectroscopy, PET = Positron emission tomography, PRx = Pressure reactivity index, TCD = Transcranial Doppler, Xe-CT = Xenon-enhanced computed tomography.

When the original ICP protocols are transferred from TBI there are some important aSAH-related issues that need to be considered. First, regarding indication, ICP-monitoring is chiefly considered in TBI patients with Glasgow coma scale score ≤ 8 . In aSAH patients, ICP-monitoring is applied more liberally also in less unconscious patients since ICP may be increased due to CSF disturbances also before ventricular dilatation appears. CSF treatment may even be used in drowsy but conscious aSAH patients in case of symptomatic acute hydrocephalus. Second, regarding ICP monitors, the EVD, with the possibility to drain CSF, is consistently used in aSAH, since CSF disturbances and acute hydrocephalus are such prominent etiologies for ICP elevations. Third, the ICP-thresholds that warrant treatment are not as investigated in aSAH as in TBI. There are some studies that have demonstrated that aSAH patients with longer monitoring episodes of ICP above 20–25 mmHg exhibit an increased risk of clinical deterioration,⁵ worse cerebral energy metabolism,¹² unfavorable outcome,^{6,21} and mortality.¹⁹ These thresholds would be in accordance with those established in TBI.^{11,22} Fourth, regarding ICP-lowering treatments, aSAH patients may benefit much more from CSF-drainage with an EVD than in TBI, considering that the dominating reason for increased ICP is CSF disturbances and acute hydrocephalus. Hyperventilation is used in TBI to lower ICP by cerebral vasoconstriction,²³ which may be more dangerous in aSAH due to the high incidence of concurrent vasospasm (see 3.1.2). Barbiturates and decompressive craniectomy (DC) are occasionally last-tier life-saving treatments in aSAH, but there is no clear evidence if they improve clinical outcome in aSAH.^{17,24,25} Both barbiturates and DC have more established roles as last-tier ICP-treatments in TBI,^{11,26,27} although the role of DC has been challenged also in TBI.^{28,29} Lastly, in TBI, there are some studies that support the use of individualized ICP-thresholds, defined as the ICP-level when cerebral autoregulation becomes severely deranged,^{30,31} but this remains to be investigated in aSAH.

Altogether, despite that ICP-elevations are frequent and escalated treatments protocols are warranted, there is currently a lack of high-quality studies as well as guideline recommendations in this area for aSAH. There is some support that many aspects of the TBI protocols may be extrapolated to aSAH,^{12,21} but there are many pertinent disease-specific differences that need to be further elucidated regarding optimal ICP-treatment thresholds and optimal treatment options and their order of escalation. MMM tools may carry a role to determine when cerebral decompensation occurs due to high ICP and to evaluate successful effects of treatments, but the evidence to support this approach is very limited.

3.1.2. Carbon dioxide management: a balance between intracranial pressure and cerebral blood flow optimization

Several studies of aSAH support normo- and even hypercapnia in order to counteract ischemic CBF,³² increase brain tissue oxygenation,³² reduce DCI,³³ and improve clinical outcome.^{33–35} However, the literature is not completely consistent, as others have rather found that mild hyperventilation (pCO₂ 4.0–5.1 kPa) may be the optimal balance to avoid last-tier ICP treatments, DCI, and poor outcome.³⁶ Particularly, one fear with too generous hypercapnia is steal phenomenon, i.e. CBF augmentation only in pCO₂-reactive brain regions that were already non-ischemic, while vasospastic and ischemic brain regions with lost pCO₂-reactivity instead exhibit a CBF decrease.³⁷ On balance, a pCO₂ between 4.5 and 5.5 kPa may be an adequate balance among high ICP, low CBF, and the risk of steal. Radiological imaging such as xenon-enhanced computed tomography^{38–40} and MMM-tools including btO₂/jugular bulb and microdialysis may be of value to better determine the cerebral net effects of therapy changes in pCO₂-ventilation, although spatial constraints to focal brain regions may limit the sensitivity of btO₂ or microdialysis to detect the any potential negative steal effect in distant, vulnerable brain regions.

Table 2

Monitoring variables, target intervals, and treatments in aSAH – international guidelines (AHA, NCC), local practices (Uppsala), and comparison with TBI (BTF).

| Variable | Target interval | Treatment |
|--|---|--|
| ICP | AHA: CSF drainage with an EVD or a lumbar drainage in case of acute hydrocephalus ³ NCC: None ⁴ Uppsala: ICP ≤20 mm Hg ⁵ BTF: ICP ≤22 mm Hg ¹¹ | Head elevation Hematoma evacuation Hyperventilation CSF drainage Sedation Barbiturates Decompressive craniectomy |
| ABP/CPP i) before aneurysm occlusion ii) after aneurysm occlusion | AHA: i) avoiding systolic blood pressure (sBP) above 160 mmHg. ii) euvolemia, no strict ABP-/CPP-target ³ NCC: i) avoiding MAP above 110 mmHg. ii) euvolemia, no strict ABP-/CPP-target ⁴ Uppsala: i) sBP 120–160 mmHg and CPP ≥60 mmHg. ii) CPP ≥60 mmHg ⁵ BTF: i) and ii) not applicable. ii) CPP between 60 and 70 mm Hg ¹¹ | ICP control (above) Intravenous fluids Vasopressors Antihypertensives |
| CBF pressure autoregulation | AHA: No target ³ NCC: No target ⁴ Uppsala: No target ⁵ BTF: No target ¹¹ | CPP optimum |
| CBF | AHA: No target ³ NCC: No target ⁴ Uppsala: No target ²⁰ BTF: No target ¹¹ | CPP-, pCO ₂ -, and autoregulation management |
| Arterial oxygenation | AHA: RBCT may be beneficial for aSAH patients at risk of cerebral ischemia. No specific HgB or pO ₂ target ³ NCC: HgB above 8–10 g/dL. No specific pO ₂ target ⁴ Uppsala: Hgb >10 g/dL and pO ₂ ≥ 12 kPa ⁵ BTF: No target ¹¹ | Respiratory optimization Minimize blood loss Red blood cell transfusion |
| Arterial glucose | AHA: No specific target, but avoid hypoglycemia ³ NCC: 4.4–11.1 mM ⁴ Uppsala: 5–10 mM ⁵ BTF: No target ¹¹ Tight glycemic control: 4.4–6.1 mM ⁸¹ | Intravenous glucose Insulin injection/infusion |
| Cerebral oxygenation | AHA: No target ³ NCC: No target ⁴ Uppsala: No target ⁵ BTF: No target ¹¹ | CBF and arterial oxygenation management |
| Cerebral glucose | AHA: No target ³ NCC: No target ⁴ Uppsala: No target, but clinical evaluation if cerebral glucose <0.5 mM (MD) ¹⁵³ BTF: No target ¹¹ | CBF and arterial glucose management |
| Cerebral energy metabolism | MD consensus meeting 2014: Cerebral glucose >0.2–0.8 mM ⁹² AHA: No target ³ NCC: No target ⁴ Uppsala: No target, but clinical evaluation if cerebral LPR >40 (MD) ¹⁵³ BTF: No target ¹¹ MD consensus meeting 2014: Cerebral LPR <25–40 ⁹² | Optimize the variables above. |

BTF = Brain Trauma Foundation, CBF = Cerebral blood flow, CPP = Cerebral perfusion pressure, CPPopt = Optimal CPP, CSF = Cerebrospinal fluid, ICP = Intracranial pressure, LPR = Lactate-/pyruvate ratio, MD = Microdialysis.



Fig. 2. Illustration of a multimodality monitoring case in an aSAH patient.

The figure shows an example of multimodality monitoring in aSAH at our center. This aSAH patient was unconscious, intubated, and mechanically ventilated and had therefore received an EVD (*) for ICP monitoring and cerebral microdialysis (**) for energy metabolic monitoring. Xe-CT imaging was conducted during NIC to estimate global and focal CBF. In addition, CDO₂ could be calculated based on CBF and the concurrent CaO₂. This type of MMM setup can be used to diagnose the specific cause for imminent cerebral energy metabolic failure, by evaluating concurrent global/focal cerebral ischemia and CDO₂. As illustrated, there is significant regional CBF variation, which limits the global validity of focal monitors such as the microdialysis.

aSAH = Aneurysmal subarachnoid hemorrhage, CBF = Cerebral blood flow, CaO₂ = Arterial content of oxygen, CDO₂ = Cerebral delivery of oxygen, EVD = External ventricular drainage, MMM = Multimodality monitoring, NIC = Neurointensive care, Xe-CT = Xenon-enhanced computed tomography.

3.1.3. ABP-, CPP-, and cerebral autoregulation monitoring, thresholds, and treatments

ABP- and, in the aSAH cases with an EVD, CPP-monitoring are very important during NIC.⁴¹ In aSAH care, there is a biphasic approach to target ABP and CPP. Re-bleeding is a severe early complication and the highest risk is estimated to occur within the first 24 h post-ictus.⁴² Elevated ABP is thought to be an important risk factor for re-bleeding, although more aggressive ABP-lowering management has not shown any definite outcome benefit.⁴³ Currently, AHA recommends avoiding systolic blood pressure (sBP) above 160 mmHg³ and NCC recommends that mean arterial blood pressure (MAP) above 110 mmHg should be avoided until aneurysm occlusion.⁴

After a successful aneurysm occlusion, the risk/benefit ratio of high ABP/CPP changes, since the re-bleeding risk is almost obviated, whereas there is a gradual increase in the risk of cerebral vasospasm, delayed cerebral ischemia (DCI), and brain infarctions during the following 10–14 days. Both AHA and the NCC recommend to maintain euvolemia to prevent cerebral ischemia and to induce arterial hypertension in case of DCI, but without any strict ABP-/CPP-threshold.^{3,4} Due to the lack of strict guideline recommendations in ABP-/CPP-targets,^{3,4} many centers extrapolate the CPP-targets from TBI protocols and keep the lower threshold target at 60 mmHg.^{5,11} However, current evidence support that much higher CPP-targets may be warranted in aSAH (Fig. 3). Findings from retrospective studies by our as well as other groups have demonstrated that CPP closer to 70–90 mmHg is associated with better brain tissue oxygenation,¹⁴ cerebral energy metabolism,^{12,14} and favorable outcome^{6,21} in aSAH.

However, the role of fixed CPP-targets for all patients has also been questioned, due to differences in cerebral autoregulation between patients and throughout the temporal course in the acute phase (Fig. 4). For example, many aSAH patients exhibit co-morbidities such as chronic arterial hypertension, leading to a chronic right-shifted autoregulation curve. This means that the lower and upper limit of autoregulation are pushed towards higher baseline ABP-/CPP-values, predisposing for greater susceptibility for cerebral ischemia at ABP-/CPP-values that healthier patients would tolerate.⁴⁴ Additionally, aSAH patients exhibit various degrees of cerebral vasospasm throughout the vascular tree, which may also vary over time in the acute phase. The importance of an individual and temporally dynamic cerebral pressure autoregulatory status has encouraged the development of MMM tools to assess this function, including pressure reactivity index (PRx), mean flow index (Mx), and

oxygen reactivity index (ORx).⁴⁴ Particularly, when PRx is plotted against CPP, an autoregulation curve with the optimal plateau phase of stable CBF can oftentimes be estimated (denoted as CPPopt). CPPopt as a treatment target has shown promising results in TBI studies,⁴⁵ in which CPP close to CPPopt has been associated with optimal btO_2 ,⁴⁶ cerebral energy metabolism,⁴⁷ and clinical outcome.^{47–51} However, the evidence to support CPPopt in aSAH is less clear. Some studies have found that CPP below CPPopt is associated with lower CBF^{8,52} and precedes DCI,⁵³ whereas CPP above CPPopt seems to provoke hyperemia and seizures,⁵⁴ but it does not correlate with cerebral energy metabolism¹² or unfavorable outcome.²¹

Altogether, several retrospective studies support that aSAH patients may benefit from much higher CPP-targets closer to 70–90 mmHg, but there is a need for prospective studies to validate this and determine the best methods to reach these targets, e.g. ABP augmentation by fluids and vasopressors and/or different methods of ICP-lowering. There are preliminary reports of individualized autoregulatory CPP-targets, but their role in aSAH remains to be determined.

3.2. Oxygenation – arterial content, cerebral delivery, and cerebral tissue oxygenation

Previous sections have focused on CBF and this section will discuss the variables responsible for the arterial oxygen content (CaO_2), with the ultimate goal to optimize CDO_2 . The hemoglobin (Hgb) level is the main contributing factor for CaO_2 in case of near maximal oxygen saturation (SaO_2), whereas the freely dissolved oxygen only make up a small proportion of the CaO_2 . Anemia therefore drastically reduces CDO_2 . At the same time, hemodilution is one of the components in HHH-therapy to improve blood rheology and increase CBF,⁸ although the net benefit on CDO_2 could be questioned.⁸ The definition of anemia and the threshold for red blood cell transfusion (RBCT) during NIC, the net cerebral effects of hemodilution, and the role of arterial hyperoxia have received great interest in acute brain injuries in general as well as in aSAH, as discussed below.

3.2.1. The role of hemoglobin

Regarding the definition of significant anemia in aSAH, several retrospective studies demonstrate an increased risk of developing brain tissue hypoxia,^{55,56} cerebral energy metabolic disturbances,^{55,56} and poor neurological outcome⁵⁷ when Hgb falls below 9–10 g/dL. However,

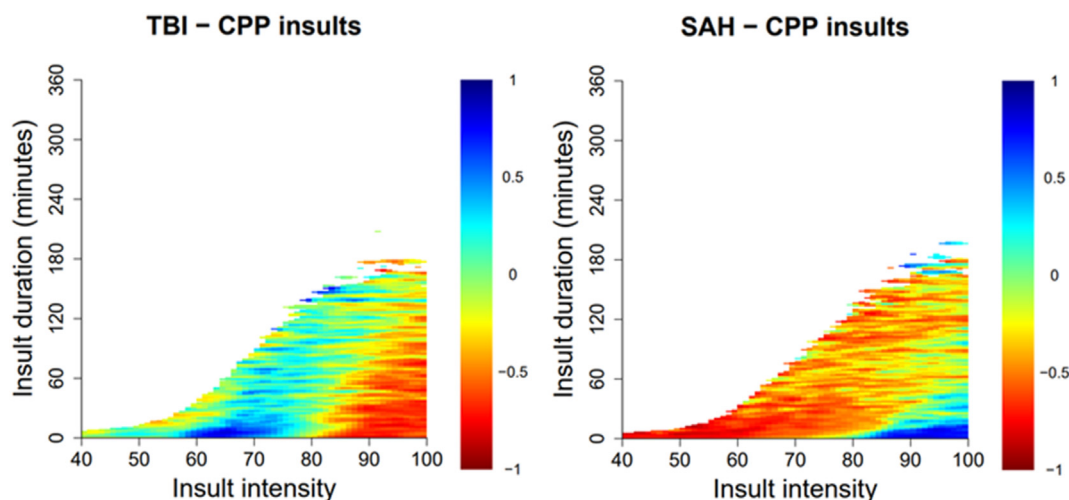


Fig. 3. CPP in relation to clinical outcome in TBI and SAH.

The figure illustrates the combined effect of “insult” duration and intensity on clinical outcome.⁶ Red and blue color indicate unfavorable and favorable clinical outcome, respectively, in a subset of TBI ($n = 441$) and aSAH ($n = 449$) patients treated at our center. The patients were managed with similar treatment targets (CPP ≥ 60 mmHg) and the graphs illustrate that aSAH patients may benefit from much higher CPP-targets than TBI patients. aSAH = aneurysmal subarachnoid hemorrhage. CPP = Cerebral perfusion pressure. TBI = Traumatic brain injury.

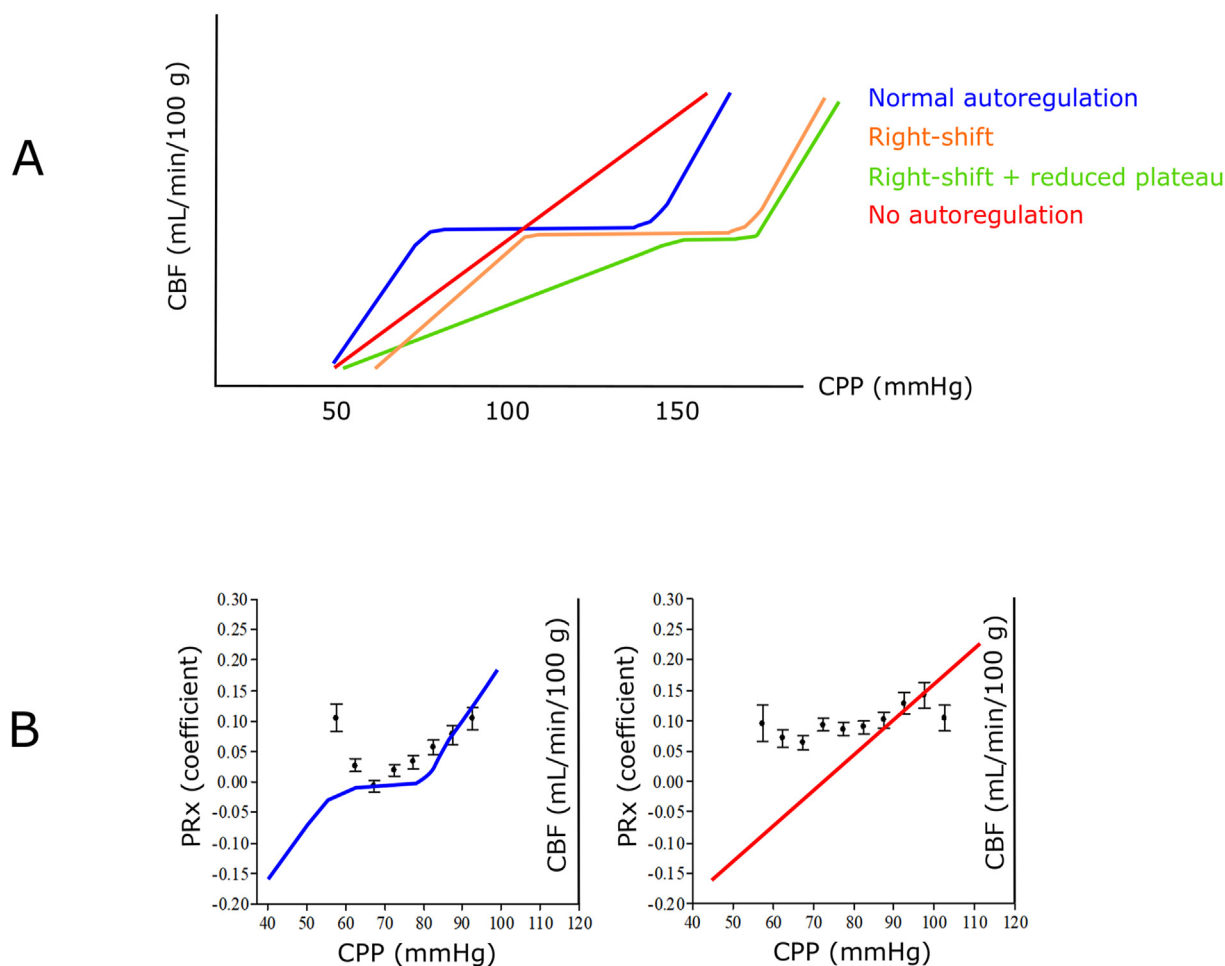


Fig. 4. A–B. Key concepts in cerebral pressure autoregulation and autoregulatory-oriented therapy.

Fig. 4A illustrates four examples of different cerebral pressure autoregulatory status. The *blue curve* shows the classic “Lassen curve” with a plateau of stable CBF over a broad range of CPPs. Cerebral ischemia occurs at the lower end of autoregulation when the cerebral vessels are already maximally dilated and then become pressure passive below this CPP-value. Similarly, cerebral hyperemia occurs as CPP surpasses the upper end of the autoregulatory plateau, when the capacity for further cerebral vasoconstriction is exceeded, and CBF again follows CPP passively. The *yellow curve* shows a right-shifted curve with preserved plateau range, which could be the case for patients with pre-ictal chronic arterial hypertension. The *green curve* illustrates a case with right-shifted and narrowed plateau, which may occur with cerebral vasospasm with increased vasoconstriction and reduced capacity for vasodilation. Hence, both the *yellow* and *green curves* illustrate two cases with increased susceptibility for cerebral ischemia despite “normal” CPP. The *red curve* illustrates a case with totally lost capacity to autoregulate, where CBF completely depends on CPP. Fig. 4B illustrates how the capacity for cerebral pressure autoregulation curve may be continuously monitored with PRx plotted against CPP for the last 4 h, in order to detect CPPopt. CPPopt reflects the plateau phase of CBF, i.e. the nadir of the U-shaped PRx/ CPP curve. However, in cases with lost capacity to autoregulate, e.g. with high PRx and without the U-shaped curve, CPPopt cannot be detected.

CBF = Cerebral blood flow, CPP = Cerebral perfusion pressure, CPPopt = Optimal CPP, PRx = Pressure reactivity index.

general management to avoid and when to treat anemia remains controversial. NCC recommends at first hand to minimize all necessary blood loss (e.g. from lab tests) and at second hand to give RBCT to keep HgB above 8–10 g/dL and that patients with DCI might benefit from even higher levels.⁴ AHA is more vague and states that RBCT may be beneficial for aSAH patients at risk of cerebral ischemia, although any threshold for treatment is not defined.³ Hence, the most crucial question has remained if and when aSAH patients benefit from RBCT. Similar to the anemia-threshold, RBCT seems to improve cerebral oxygenation and energy metabolism and clinical outcome when HgB has fallen below 9–10 g/dL,^{57,58} but not in all studies.⁵⁹ One important concern has been if the potential improvement in cerebral oxygenation from RBCT, in effect, outweighs the treatment risks. The potential negative effects of RBCT are not fully understood, but may include a worsening in cerebral pressure autoregulation,⁶⁰ increased inflammatory response, as well as cardiac and respiratory dysfunction.^{61,62} The risks of RBCT have led to explorations of “restricted” (HgB 7 g/dL) rather than “liberal” (10 g/dL) thresholds for RBCT, where the more restricted approach appears safe

and even favorable at least in general ICU patients.⁶³ However, it has been questioned if this is valid for aSAH since these patients exhibit a reduced reserve for any CBF and CDO₂ deterioration, predisposing for a lower tolerance for low HgB-levels. Thus, MMM-tools could then be useful to determine when cerebral decompensation occurs and when higher HgB by means of RBCT could be warranted to individualize care. For example, RBCT might be beneficial for subnormal HgB with concurrent brain tissue hypoxia, but not in case of normal brain tissue oxygenation. Otherwise, as a solution to any potential negative effect of RBCT, other oxygen-carrying agents (e.g. SANGUINATE) have been suggested as treatments to improve cerebral oxygenation in aSAH.⁶⁴

Interestingly, hemodilution, which is part of HHH-therapy, may seem contradictory to the RBCT-approach. The idea of hemodilution is CBF augmentation to improve CDO₂, but it occurs at the expense of a lower CaO₂, and from a mechanistic point of view it is not fully clear if the CBF augmentation occurs due to improved blood rheology or is a partial compensation to counteract an increased tissue hypoxia.⁶⁵ Most aSAH studies have confirmed that hemodilution leads to higher CBF, but that it

does not translate into any CDO₂ improvement.^{8,66} Consequently, hemodilution does not benefit cerebral oxygenation, but there are perhaps other advantages of the CBF augmentation.⁶⁷ Specifically, higher CBF may increase CDGlc and in theory also clearance of cerebral waste products.

To conclude, controversy remains regarding how to optimize CaO₂ in aSAH. Both RBCT and hemodilution remain two apparently contradictory treatment approaches for DCI. However, in theory, it may be that RBCT is beneficial in case of brain tissue hypoxia to improve CDO₂, whereas the CBF augmentation may be more relevant when the predominant pathomechanism is mitochondrial dysfunction in order to drive anaerobic energy metabolism. MMM-protocols could then be of value to further diagnose the cause of energy metabolic disturbance in order to individualize CBF- and CaO₂-oriented treatments.

3.2.2. Arterial oxygenation

As already outlined, changes in the partial pressure of oxygen (pO₂) has a great influence on CaO₂ when the SaO₂ is low, but not under normal settings with near full saturation. Otherwise, the effects of supranormal pO₂ on the freely dissolved oxygen content is negligible for CaO₂. Although NCC and AHA do not provide any guidelines for pO₂,^{3,4} most centers aim for normoxia.^{5,35} There has also been an interest in normobaric hyperoxia as a way to compensate for cerebral ischemia and diffusion limitations to improve cerebral oxygenation and aerobic energy metabolism. In effect, increasing FiO₂ to hyperoxic levels in order to treat low btO₂ has shown promise in TBI,^{68,69} however hyperoxic pO₂-levels may also exert adverse effects including cerebral vasoconstriction^{70,71} and induction of reactive oxygen species.⁷² In aSAH, the negative effects of hyperoxia seem to predominate, as hyperoxia has been associated with cerebral vasospasm,⁷³ DCI,^{74,75} and unfavorable outcome.⁷⁴⁻⁷⁶ Altogether, normoxia around 12 kPa with near maximal oxygen saturation seems most beneficial. However, it remains to be determined if hyperoxia is only negative or may be beneficial in certain clinical states of e.g. diffusion limitations due to edema or to overcome mitochondrial dysfunction, based on MMM-analysis.

3.3. Cerebral delivery of nutrients

The content of the arterial nutrients glucose and lactate together with CBF determine the CDGlc and CDLac. In this section, optimization of the arterial content of glucose and lactate are discussed in detail.

3.3.1. Arterial glucose thresholds and management

The arterial glucose content is under normal conditions regulated within a narrow interval, but aSAH typically induces an acute and often persistent elevation in arterial glucose post-ictus due to activation of the hypothalamic-pituitary-adrenal (HPA)-axis, hypothalamic damage/dysfunction, and systemic inflammation.^{35,77-79} Stress-induced hyperglycemia may compensate for eventual low CBF in order to attenuate neuroglucopenia, but hyperglycemia may also exert several negative systemic and cerebral effects. Particularly, hyperglycemia increases the risk of systemic complications including infections, disturbed wound healing, and respiratory dysfunction.^{77,80,81} In addition, hyperglycemia is associated with disturbed cerebral energy metabolism⁸² and development of DCI,⁸²⁻⁸⁴ possibly due to more vasospasm, microvascular thrombi, increased systemic inflammation, and exacerbated reperfusion injury.⁷⁷ Several studies have also established an association between hyperglycemia and unfavorable clinical outcome in aSAH.^{35,79,82,83} Consequently, optimizing arterial glucose is of great importance and this subject has received much interest and also led to great controversy both in general intensive care unit populations^{80,81} as well as after acute brain injury⁸⁵⁻⁸⁸ including aSAH.^{89,90} Specifically, intensive insulin therapy (IIT) to keep arterial glucose within a tight interval (e.g. 4.4-6.1 mM) leads to a significant reduction in mean arterial glucose-levels, but also increases the incidence of hypoglycemia.⁹⁰ Patients with aSAH are very vulnerable to hypoglycemia and the gain in avoiding hyperglycemia is

likely off-set by the corresponding increase in hypoglycemic events from IIT.⁹⁰ Systemic continuous glucose monitoring could facilitate IIT by earlier detection of imminent hypoglycemia, but the reliability of these continuous monitors has been questioned.⁹¹ In addition, as a way to individualize care, it has been suggested to guide arterial glucose management based on microdialysis monitoring of cerebral glucose, e.g. by administration of intravenous glucose infusion in cases of low MD-glucose.⁹² However, this has not been sufficiently studied to implement in clinical practice.

Currently, a more loose and less intense arterial glucose management is generally favored, as NCC recommends to keep it between 4.4 and 11.1 mM and possibly to adjust this based on low microdialysis-levels,⁴ whereas AHA generally recommends avoiding hypoglycemia.³ A combination of a more reliable technique to continuously measure systemic glucose combined with cerebral microdialysis-glucose monitoring could perhaps further refine arterial glucose management.

3.3.2. Arterial lactate

The role of lactate as a cerebral fuel has gradually gained acceptance and interest. Lactate is transported via monocarboxylate transporters into endothelial cells and astrocytes via MCAT1 and into neurons via MCAT2.⁹³ In the astrocyte-neuron-lactate-shuttle (ANLS), astrocytes metabolize glucose into lactate, which is shuttled to neurons and is there used for oxidative phosphorylation.⁹³⁻⁹⁷ Under normal conditions, the arterial contribution to cerebral lactate is low around 10%, but increases to 60% at 5 mM.⁹⁸ However, the cerebral lactate uptake can be up-regulated following acute brain injury.⁹⁷ As the cerebral lactate increases, more is used as cerebral energy fuel, which spares glucose.^{95,99,100} Still, the use of exogenous lactate as a supplementary cerebral energy fuel remains exploratory at the moment. However, it is worth mentioning that lactate solutions may exert additional cerebral effects. High arterial lactate may induce cerebral vasodilation and augment CBF,^{99,101} although possibly at the expense of a worse pressure autoregulation.^{35,102} Furthermore, lactate in hypertonic solutions may be beneficial to reduce brain edema and thereby reduce ICP.⁹⁵ Altogether, further MMM studies are needed to better determine the role of exogenous lactate infusions on cerebral physiology.

3.4. Cerebral energy metabolism

CaO₂, CaGlc, CaLac, and CBF are important variables to optimize the cerebral energy metabolic supply for neuronal survival. However, there are several additional variables that interfere with the capacity to generate energy as well as the requirements of energy metabolic turnover, as described below.

3.4.1. Hypo- and hyperthermia – temperature management

The body has under normal conditions a tightly regulated set-temperature around 37 °C. There is controversy over the exact definitions of hypo-, normo-, and hyperthermia in the literature, however, T < 36 °C, 36 °C ≤ T ≤ 38, and T > 38 °C would be one example applied by our institution.^{21,103} In addition, systemic and brain temperature are usually highly correlated, but brain temperature may be up to 1-2 °C higher following acute brain injury,¹⁰⁴ secondary to elevated heat production from increased energy metabolism.

The natural course of body temperature follows a biphasic pattern after aSAH. Particularly in poor-grade cases with transient global ischemia, body temperature initially falls, possibly as a neuroprotective mechanism, the first hours and then hyperthermia usually gradually develops.¹⁰⁵ Major drivers of hyperthermia are infectious complications during NIC and neurogenic mechanisms. Neurogenic fever is common in poor-grade cases with a greater burden of SAH and IVH¹⁰⁶ and the underlying explanation is a change in temperature set point due to toxic and inflammatory effects of the SAH/IVH and/or ischemic complications in the brainstem and hypothalamus.¹⁰⁷

Several previous studies demonstrate an association between

hyperthermia and negative outcomes in aSAH, including worse cerebral energy metabolism,¹⁰⁸ development of DCI,^{106,109} and poor neurological recovery.^{21,106,109,110} One explanation is that hyperthermia, per se, induces negative cerebral effects including increased cerebral energy metabolism, cerebral hyperemia, blood-brain-barrier disruption and cerebral edema, intracranial hypertension, and excitotoxicity.¹¹¹ However, the direction of the association between hyperthermia and poor aSAH outcomes is not always clear and hyperthermia is to a great extent also an epiphenomenon of a worse primary and secondary brain injury. Current guidelines recommend avoiding hyperthermia, although the treatment threshold and therapeutic approaches remain largely varied among guidelines and centers. AHA provides a recommendation to avoid hyperthermia in general by using standard treatments, without any further specifications.³ NCC recommends avoiding hyperthermia (without any strict threshold), particularly in the vasospasm phase, by using acetaminophen and NSAIDs at first hand and surface cooling and intravascular devices at second hand, while avoiding shivering.⁴ The level of evidence for these treatments is low. Specifically, among the pharmacological agents, NSAIDs may reduce fever, but could simultaneously induce cerebral vasoconstriction, and worsen CPP and btO_2 , predisposing for negative net effects on the brain, in addition to risks of systemic complications (kidney injury).¹¹² Among the various cooling techniques, intravascular cooling shows some promise at least in TBI, as initiation of cooling improves cerebral energy metabolism.¹¹³ A major concern with this approach is the risk of inflicting stress and shivering, which may rather worsen cerebral physiology.¹¹⁴ Furthermore, therapeutic hypothermia has received great interest as a potential neuroprotective treatment in acute brain injuries, however, so far, any true benefit on outcome remains unclear in general as well as in aSAH. Specifically, in aSAH, therapeutic hypothermia has been mostly studied as an intraoperative neuroprotective adjunct during surgery for ruptured intracranial aneurysms, which was shown to be safe, but did not improve neurological outcomes.^{115,116} AHA does currently not recommend it on a general basis, but holds it as an option.³ Otherwise therapeutic hypothermia has been used to treat DCI¹¹⁷ and elevated ICP¹¹⁸ in case series, but without any conclusive evidence for its use. Similarly, although therapeutic hypothermia initially seemed promising in TBI,¹¹⁹ recent studies have shown that hypothermia neither improves outcome if used to reduce intracranial hypertension prophylactically¹²⁰ or therapeutically.¹²¹ Similarly, after cardiac arrest, initial studies found promising neurological results with therapeutic hypothermia,¹²² whereas more recent studies indicate that this treatment does not improve functional outcomes.¹²³

Altogether, hyperthermia is common during the late acute phase of aSAH and is associated with negative outcomes, but the causality remains obscure. Currently, hyperthermia is chiefly treated on a symptomatic physiological basis. Particularly in non-infectious, neurogenic hyperthermia, the underlying mechanism is not addressed. It is possible that more granular studies based on protein biomarkers from CSF-/MD-samples^{9,10} may provide a better understanding of underlying processes such as neuroinflammation and may provide a mechanistic basis for future treatments.

3.4.2. Seizures and cortical spreading depolarizations

Epileptic activity is common following acute brain injuries in general as well as after aSAH. This may manifest as focal or generalized convulsive and non-convulsive seizures. Seizures occasionally occur immediately after ictus or re-bleeding and in case of cerebral ischemia and brain herniation.¹²⁴ Convulsive seizures are typically easy to identify, whereas non-convulsive seizures are rather detected with electroencephalography (EEG) in patients in a poor neurological condition without any other clear explanation.¹²⁵ The rate of seizures based on clinical criteria has been estimated to occur in between 4 and 26% of the cases,¹²⁴ whereas the rate of epileptic activity may be much higher as evaluated with EEG and in particular with the more sensitive method electrocorticography.¹²⁶ Seizures may increase ICP and energy metabolic

turnover leading to neuronal cell death.¹²⁷ Both AHA and NCC state that short-term seizure prophylaxis may be considered in the acute phase,^{3,4} although NCC points out that phenytoin has been associated with worsened long-term outcome and should be avoided.⁴ NCC also suggests the use of continuous EEG to assess for non-convulsive seizures in patients who fail to improve.⁴

A distinct, but akin neuroelectric phenomenon is cortical spreading depolarization (CSD), characterized by a moving gradient of cortical membrane depolarization with subsequent electrical depression and associated CBF disturbances (inverse neurovascular coupling).¹²⁷⁻¹²⁹ This may ultimately result in disturbed cerebral energy metabolism and cell death. There are currently no specific treatments for CSD, but it has generally been suggested beneficial to optimize systemic and cerebral physiology. Furthermore, glutamate seems to be a major contributor to CSD and various pharmacological agents targeting glutamate synthesis and receptor-antagonists have also been suggested.¹²⁷

In conclusion, this is an emerging areas of NIC, studies of CSD, and the role of the newer generation of antiepileptic agents with better tolerance profiles are much warranted.

3.4.3. Mitochondrial dysfunction

Energy is produced via anaerobic glycolysis and aerobic oxidative phosphorylation, in which the former only generates a small proportion of the total energy production. Functioning mitochondria are therefore key for energy production. In recent years, the understanding of mitochondrial dysfunction as a pathophysiological mechanism in acute brain injuries including aSAH has gained increased understanding and interest.^{67,130,131} Microdialysis studies indicate that mitochondrial dysfunction is common after aSAH^{67,132} and is associated with poor clinical outcome.¹³³ It has been speculated if arterial hyperoxia could improve oxidative aerobic energy metabolism in the mitochondria.¹³⁴ Pharmacological agents such as cyclosporin have been tried as potential neuroprotective agents to ameliorate this pathological energy metabolic state in TBI studies,¹³⁵ but there are otherwise no current available therapies during NIC. This is also an emerging field that needs better understanding and therapeutic agents.

4. Cellular and molecular injury processes and the role of neuroprotective agents

Cerebral physiology as well as cellular and molecular injury patterns compromise a very complex area that currently remains insufficiently understood. There have been several attempts to develop and implement neuroprotective agents in aSAH, but with limited success, similar to the case in severe TBI. Some explanations for the disappointing results may be animal/patient heterogeneity and differences in therapeutic windows between animal models and human trials. A deeper understanding of the cellular and molecular injury patterns together with MMM-tools to monitor these processes bedside could potentially solve this problem, as discussed below.

4.1. Neuroprotective agents

There are a number of clinical trials that have evaluated different pharmacological agents to address various aspects of aSAH pathophysiology.¹³⁶ First, nimodipine is a calcium-channel blocker, which reduces DCI and improves outcome, and is the only neuroprotective agent that is integrated in current management guidelines.^{3,4,137} The mechanism of action was initially thought to counteract cerebral vasospasm, which proved not to be the case,¹³⁷ and other important but less understood mechanisms may be more important. Second, endothelin-receptor antagonists have proven to counteract cerebral vasospasm, but without any benefit on clinical outcome, possibly as a consequence of associated adverse effects such as anemia, arterial hypotension, and respiratory failure.¹³⁸ Third, other agents with a potential beneficial effect on cerebral vasospasm and DCI include statins^{139,140} and magnesium

sulphate,¹⁴¹ which, so far, are promising but need further validation.^{3,4} Fourth, mitochondrial dysfunction is common after aSAH⁶⁷ and as outlined above, cyclosporin has been used to treat this condition in TBI,¹³⁵ but it remains to be tested in aSAH. Fifth, there are several emerging agents such as cilostazol that may exert broad-spectrum beneficial neuroprotective effects that need to be further explored in future randomized controlled trials.¹⁴⁰ Sixth, although tranexamic acid is not directly neuroprotective, it could be viewed as that in one sense, since administration after ictus until aneurysm occlusion may reduce the rate of re-bleedings and thereby secondary brain injury. However, concerns have also been raised regarding increased risk of thromboembolic complications with this treatment^{136,142,143} and with modern management including early aneurysm occlusion it does not seem to add any benefit on long-term outcome.¹⁴²

4.2. Online bedside monitoring of molecular injury patterns – the next step in precision medicine?

The development of large-pore microdialysis catheters has paved the way to monitor and analyze complex molecular cascades in the interstitial tissue of the brain bedside.^{144–148} Together with the newly developed technique proximity extension assay (PEA),^{9,10,149} which is a very sensitive tool to detect small quantities of protein while using only small volumes of fluid, it is now also possible to efficaciously detect and study numerous brain protein biomarkers from patients with acute brain injury such as TBI and aSAH.^{150–152} This may enable a deeper understanding of ongoing pathophysiological processes and refine indications and time windows of treatments for neuroprotective pharmacological agents. However, due to the complexity of these data, there will most likely be a need to analyze the dynamics of these biomarkers with artificial intelligence to understand their complex patterns, in future NIC units.

5. Concluding remarks

Although the level of evidence in aSAH management in general is poor, we do know several ways to improve outcome, such as early aneurysm occlusion to prevent re-bleeding, CSF drainage in case of increased ICP and/or acute hydrocephalus, and CBF augmentation in case of DCI. In addition, NIC with the aim to avoid secondary insults has successfully improved clinical outcome after aSAH. However, as outlined in this review, it has been very challenging to prove which specific NIC targets and treatments that are most optimal. This is not surprising, considering the challenges in conducting research in such a severe disease as aSAH which is often associated with a heterogeneous and complex NIC course. Most likely, CPP above 60 mmHg, ICP below 20 mmHg, and oxygen saturation above 95% are good rough estimates to optimize cerebral physiology, but we argue that NIC management could be further fine tuned. Below, we highlight four future perspectives, escalated from what hopefully lies just next-door (short-term) to what may be discerned a bit farther away on the horizon (long-term).

- i) NIC management of aSAH is currently to a large degree extrapolated from TBI care. However, we need to proceed with basic aSAH-specific prospective studies on high-frequency data analyses of ICP, CPP, Hgb, and body temperature etc. to better understand general, “epidemiological (for all patients)” pathophysiology and treatment effects in this disease.
- ii) The approach above is still limited to the one-size-fits-all concept and the next step is to individualized care. This can be done by integrating more systemic and cerebral physiology from MMM-tools into NIC management, such as autoregulatory-oriented therapy with CPPopt.
- iii) The major challenges of implementing MMM tools in management are their limitations regarding reliability and validity. We need to proceed to study cerebral physiology in relation to these

inherent limitations of MMM tools and proceed with methodological innovation. Artificial intelligence may prove to be beneficial in this attempt.

- iv) A major step towards MMM development and individualized treatments is to go from the physiological to the cellular and molecular level of cerebral injury mechanisms. Large-pore cerebral microdialysis with bedside online measurements of biomarkers related to neuroinflammation, neurodegeneration, and neurorepair may be one solution in this direction. Specifically, this may be of great importance in order to optimize the indication and time window for future neuroprotective pharmacological agents.

Declaration of competing interest

The authors declare no conflict of interest.

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Abbreviatipons

- ABP =: Arterial blood pressure
 AHA =: American Heart Association
 ANLS =: Astrocyte-neuron-lactate-shuttle
 aSAH =: Aneurysmal SAH
 BrO₂ =: Brain tissue oxygenation
 CaO₂ =: Arterial oxygen content
 CBF =: Cerebral blood flow
 CDGlc =: Cerebral delivery of glucose
 CDLac =: Cerebral delivery of lactate
 CDO₂ =: Cerebral delivery of oxygen
 CPP =: Cerebral perfusion pressure
 CPPopt =: The optimal CPP, i.e. with the most optimal autoregulatory status (lowest PRx)
 CSD =: Cortical spreading depolarization
 CSF =: Cerebrospinal fluid
 DC =: Decompressive craniectomy
 DCI =: Delayed cerebral ischemia
 EEG =: Electroencephalography
 EVD =: External ventricular drainage
 Hgb =: Hemoglobin
 HHH =: Hypervolemia, hemodilution, and hypertension
 HPA =: Hypothalamic-pituitary-adrenal
 ICH =: Intracerebral hemorrhage
 ICP =: Intracranial pressure
 IIT =: Intensive insulin therapy
 IMPACT =: International mission for prognosis and analysis of clinical trials in TBI

IVH =: Intraventricular hemorrhage
MMM =: Multimodality monitoring
NCC =: Neurocritical Care Society
NIC =: Neurointensive care
NSAID =: Non-steroidal anti-inflammatory drugs
PEA =: Proximity extension assay

PRx =: Pressure reactivity index
RBCt =: Red blood cell transfusion
SAH =: Subarachnoid hemorrhage
SaO₂ =: Arterial oxygen saturation
sBP =: Systolic blood pressure
TBI =: Traumatic brain injury