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# Проблеми анестезіології та інтенсивної терапії

## Problems of Anesthesiology and Intensive Care

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### BRAIN PROTECTION STRATEGIES AND CONTROVERSIES

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#### СТРАТЕГИИ И ОБСУЖДЕНИЯ МОЗГОВОЙ ПРОТЕКЦИИ

**Актуальность.** Окислительный стресс — главный фактор в повреждении мозга, который инициирует события, приводящие к затяжной нейрональной дисфункции и ремоделированию. Важно отметить, что антиоксиданты могут защитить мозг от окислительного повреждения, модулируя его способность справляться с синаптической дисфункцией и когнитивными нарушениями. Но мы также должны рассмотреть другие способы защиты ткани головного мозга от последствий внутричерепных опухолей, ишемии головного мозга или черепно-мозговой травмы.

**Методы.** Аномалии церебрального кровотока (например, у пациентов с вазоспазмом после субарахноидального кровоизлияния или внутричерепной гипертензии) требуют индивидуализированного подхода в управлении церебральным перфузионным давлением (ЦПД). В настоящее время выделяют две различные стратегии управления ЦПД, и обе они являются попыткой сохранить перфузию головного мозга на адекватном уровне, чтобы покрывать мозговые метаболические потребности. Эти тактики различаются по отношению к уровню ЦПД, и их целесообразность проявляется в зависимости от индивидуально-го статуса ЦПД, ауторегуляции и состояния гематоэнцефалического барьера.

**Выводы.** Большое количество периоперационных патофизиологических событий у пациентов, готовящихся к плановому лечению аневризмы головного мозга, требует поддержания гомеостаза путем нормотензии, нормоволемии, нормоксии, нормокапнии, нормотермии и нормогликемии. Кроме того, допустимо использование орально нимодипина. Существует достаточно доказательств, что использование магния, статинов, эритропоэтинов, стероидов, трипл-Н и интраоперационной гипотермии не эффективно.

**Ключевые слова:** повреждение мозга, церебральное перфузионное давление, саморегуляция, аневризма.

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**Relevant.** Oxidative stress is the principal factor in brain injury that initiates the events that result in protracted neuronal dysfunction and remodeling. Importantly, antioxidants can protect the brain against oxidative damage and modulate the capacity of the brain to cope with synaptic dysfunction and cognitive impairment. But also we need to review other ways to protect brain tissue after intracranial tumors, cerebral ischemia, or traumatic brain injury.

**Methods.** Cerebral blood flow abnormalities (e. g. in patients with vasospasm following subarachnoid hemorrhage or intracranial hypertension) require individualized approaches in managing CPP: Currently, two different CPP management strategies (philosophies) attempt to maintain cerebral perfusion at a level adequate to fuel the cerebral metabolic needs. Although both of these concepts

differ with respect to the level of CPP either of them may be appropriate depending of the individual status of CBF autoregulation and the blood-brain-barrier.

**Conclusions.** The plethora of perioperative pathophysiological events in patients scheduled for intracranial aneurysm surgery requires a holistic medical approach: It is essential to maintain homeostasis by controlling for normotension, normovolemia, normoxia, normocapnia, normothermia and normoglycemia. Additionally, the use of oral nimodipine is indicated. There is inadequate evidence for the treatment with magnesium and statins. Erythropoietin, steroids, triple-H and intraoperative hypothermia are not indicated.

**Key words:** brain injury, CPP, autoregulation, aneurism.

## Introduction

Patients scheduled for intracranial aneurysm clipping may present with the following clinical constellations:

- a) intact aneurysm with or without space occupying effect.
- b) ruptured aneurysm with or without cerebral vasospasm, impaired autoregulation, and/or intracranial hypertension. Thus, the perioperative anesthetic and brain protective approach is similar to concepts established for patients with intracranial tumors, cerebral ischemia, or traumatic brain injury.

## Management of cerebral perfusion pressure (CPP)

Cerebral blood flow abnormalities (e. g. in patients with vasospasm following subarachnoid hemorrhage or intracranial hypertension) require individualized approaches in managing CPP: Currently, two different CPP management strategies (philosophies) attempt to maintain cerebral perfusion at a level adequate to fuel the cerebral metabolic needs. Although both of these concepts differ with respect to the level of CPP either of them may be appropriate depending of the individual status of CBF autoregulation and the blood-brain-barrier.

1) Cascade of cerebral vasodilation and vasoconstriction (“Rosner concept”, “Edinburgh concept”) [1]: Studies in patients with severe head injury have shown that hypotension and low CPP are important factors in the generation of secondary insults. For example, the incidence, severity, and duration of arterial hypotension or  $CPP < 80$  mmHg significantly increased morbidity and mortality in these patients. The CPP approach requires intact cerebrovascular autoregulation in order to induce autoregulatory vasoconstriction for ICP control (i. e. as autoregulation is intact, elevations in CPP will produce autoregulatory vasoconstriction to maintain CBF normal while reducing intracranial blood volume and thus ICP; “Rosner concept”). This concept also applies to patients with a shift of the autoregulatory curve towards higher pressures (i. e. with “normal” CPP these patients present pressure-passive perfusion while elevations in CPP return their pressure-flow-relationship into the autoregulatory range; “Edinburgh concept”). These considerations are consistent with data in head injured patients showing fewer events with critical intracranial hypertension (plateau waves) as long a CPP was maintained with the range of 75–95 mmHg. However, target CPP values  $> 70$  mmHg is associated with an increased risk for ARDS (at least in patients with traumatic brain injury) [2].

2) Treatment of posttraumatic brain edema formation (“Lund concept”): This approach assumes defective blood-brain barrier and cerebrovascular autoregulation. As a consequence the Lund concept targets at low precapillary hydrostatic pressures and cerebral venous constriction to reduce edema formation and elevated cerebral blood volume by infusion of a) dihydroergotamine (DHE), b) the alpha-2-agonist clonidine and the beta-1-antagonist metoprolol [3] c) normalization of colloid osmotic pressure (plasma albumin concentration  $> 40$  g/l). Although there may be subgroups of patients that benefit from a reduction in precapillary hydrostatic pressure along with cerebral venous constriction there are currently no convincing data that support improved outcome with the “Lund concept”. However, target CPP values  $< 50$  mmHg are associated with an increased risk for cerebral ischemia and certainly inacceptable in patients with vasospasm,

Based on this analysts it 15 currently believed that stabilization of CPP within the range of 50–70 mmHg by means of sedation, osmодиuretics, normovolemia, and vasopressors will improve neurologic outcome in patients with ischemic challenges.

## **Anesthetics**

### *Volatile anesthetics*

Isoflurane, sevoflurane and desflurane produce maximum cerebral metabolic suppression in parallel at concentrations >2 MAC end-tidal. This effect suggests that volatile anesthetics may correct for the imbalance between oxygen supply and demand during focal cerebral ischemia. Animal studies with focal or incomplete hemispheric ischemia have shown that isoflurane, sevoflurane, and desflurane may decrease infarct size and improve neurologic outcome when given prior to the ischemic challenge. These experimental data are consistent with studies in sevoflurane anesthetized patients undergoing carotid endarterectomy showing increased tolerance to lower levels of cerebral blood flow with preserved neuronal function during carotid cross clamping when compared to halothane, or enflurane. In contrast, volatile anesthetics have no neuroprotective properties in the setting of global cerebral ischemia and when given after the insult. Sevoflurane induces minimal cerebral vasodilation when compared to isoflurane or desflurane which relates to the favourable effects of sevoflurane on ICP. In turn, sevoflurane but not isoflurane or desflurane is suitable in neurosurgical patients without exhausted intracranial elastance. Additionally, sevoflurane promoted neuroregenerative pathways by virtue of increased neuronal stem cell proliferation [4; 5]. This indicates that more modern anesthetic agents may well differ from historical drugs in their brain protective potential.

### **Hypnotics**

Studies in laboratory animals have shown that barbiturates as well as propofol reduce infarct size and improve neurologic outcome following focal or incomplete global cerebral ischemia as long as physiological variables were controlled during the experiments. In contrast, etomidate worsens neurologic outcome. While experimental data support the preventive neuroprotective effects of hypnotic agents, there is no clinical evidence to support the convincing positive data. For example, infusion of thiopental (total dose during ECC:  $39.5 \pm 8.4$  mg/kg iv) in patients undergoing cardiac surgery with normothermic cardiopulmonary bypass insignificantly reduced postoperative neuropsychological deficits Likewise, barbiturates infused to comatose patients within the first hour following cardiopulmonary resuscitation were ineffective to reduce mortality as well as neurological deficits in survivors compared to standard ICU treatment [6]. Barbiturates may also be beneficial in patients with severe head injury and refractory intracranial hypertension. This conclusion is related to a series of clinical studies where infusion of barbiturates was effective in reducing intracranial pressure and likely the mortality rate following brain trauma as long as systemic hemodynamic stability was maintained. Propofol was suggested as an alternative to barbiturates in patients undergoing cardiac surgery or for sedation following head injury due to a favorable context-sensitive half-time [7]. While propofol did not reduce neuropsychological deficits following cardiac valve surgery compared to sufentanil anesthetized patients it turned out to be more effective in treating elevated ICP with a similar neurologic outcome following head injury when compared to an opioid-based sedative regimen.

### **Anesthetics and cerebral perfusion pressure**

CPP is determined by the difference between mean arterial blood pressure (MAP) and intracranial pressure (ICP) [8]. Therefore, interpretation of anesthetic effects on CPP require characterization of their effects on both, MAP and ICP. In general anesthetic agents (barbiturates, propofol, benzodiazepines, opioids, dexmedetomidine, sevoflurane, desflurane and iso-

flurane) all decrease MAP in a dose dependent fashion. Likewise, their potential to decrease systemic hemodynamics is related to the speed of application and the pre-existing volume status of the patient. The only drug that augments systemic hemodynamics is ketamine. In contrast, barbiturates and propofol decrease ICP. Benzodiazepines, ketamine, dexmedetomidine and sevoflurane (< 1 MAC) have little to know impact on ICP. Due to their potent vasodilatory stimulation desflurane, isoflurane and nitrous oxide increase ICP secondary to increases in cerebral blood volume [10]. Therefore and in balance of the effects on MAP and ICP barbiturates and propofol may increase CPP if the administration is not associated with the decrease in MAP. While benzodiazepines and narcotic agents have little to know effect on CPP because of their net zero effects on MAP and ICP, ketamine increases cerebral perfusion pressure. Dexmedetomidine, desflurane and isoflurane decrease CPP because they either decrease MAP or do both decrease MAP and increase ICP.

### **Triple-H therapy**

The combination of induced hypertension, hypervolemia, and hemodilution (triple—H therapy) is a popular concept to prevent or treat cerebral vasospasm after aneurysmatic subarachnoid hemorrhage. Yet, the beneficial effects of triple-H therapy in these patients have never been confirmed in adequate investigations despite improved cerebral perfusion. [11] This is related to substantial side effects of triple-H including pulmonary edema, myocardial ischemia, hyponatremia, renal failure, indwelling catheter-related complications, cerebral hemorrhage, and brain edema along with triple-H.

### **Osmodiuretics**

Mannitol is an osmotic diuretic agent which decreases ICP, increases CPP, and improves CBF in laboratory animals and humans. These effects are related to plasma expansion with consecutive reduction in hematocrit, plasma viscosity, and cerebral blood volume as well as mobilization of extracellular fluids along the osmotic gradient. Treatment of intracranial hypertension using mannitol in concentrations of 0.25 — 1 g — kg (maximum: 4 g / kg > die) is more effective than the infusion of barbiturates. Likewise, bolus administration rather than continuous or prophylactic infusion as part of a rigid algorithm is recommended to control ICP. Since acute tubular necrosis may occur in response to rapid changes in the osmotic gradient plasma osmolarity must be monitored and should not exceed 320 mosmol/l. Any concern with respect to rebound-effects of mannitol (i. e. accumulation of mannitol within the extracellular space) appear to be relevant only with a defective blood-brain-barrier or duration of treatment > 4 days. Nevertheless, mannitol can be used beyond these end-points as long as critical elevations of ICP remain osmo-sensitive. As an alternative, hypertonic saline (7.5 %) may be used to control ICP. In patients with multiple injuries hypertonic saline used as “small volume resuscitation” increases arterial blood pressure in parallel to decreases in ICP. Recent clinical investigations indicate superiority of hypertonic saline over mannitol in terms of decreases in ICP and duration of effect.

### **Plasma glucose concentration**

Studies in laboratory animals and humans have shown that hyperglycemia, as well as hypoglycemia are associated with worsened outcome following cerebrovascular events or neurotrauma, The mechanisms by which normoglycemia may protect neuronal tissue include decreases in intracellular lactic acidosis along with decreases in membrane permeability and reduced edema of endothelial cells, neuroglia, and neurons. As a consequence and in a pragmatic approach avoiding hypoglycemia when infusing insulin, plasma glucose concentrations should be assayed every 2 hours and maintained within the range of 110–140 mg/dl.

### **Ca<sup>2+</sup>- channel blocker**

The proposed mechanisms of neuronal protection by Ca<sup>2+</sup>-channel blockers include cerebral vasodilation, prevention of vasospasm, reduced Ca<sup>2+</sup>-influx and modulation of

free fatty acid metabolism. Unfortunately, the results in animal models are rather contradictory. While several studies found decreases in neuronal injury and improved outcome following focal ischemia, others have failed to produce protection with Ca<sup>2+</sup>-channel blockers. Clinical trials have tested the neuroprotective effects of the L-type Ca<sup>2+</sup>-channel blocker nimodipine in patients with acute ischemic stroke and aneurysmatic or traumatic subarachnoid hemorrhage. According to a meta-analysis of 9 placebo-controlled trials with a total of 3700 patients with acute stroke oral administration of nimodipine appears to be associated with a favorable outcome as long as the treatment commences within the first 12 hours following the onset of the symptoms. However, Ca<sup>2+</sup>-channel blockers may induce arterial hypotension below the individual ischemic threshold of the patients and any relevant decrease in arterial blood pressure will reverse any potentially neuroprotective effects of the intended treatment. This may be consistent with the most recent analyses by the Cochrane Foundation who was unable to identify any beneficial effect of nimodipine in patients with ischemic stroke or traumatic hemorrhage. However, oral nimodipine may reduce the risk for poor outcome by 5.1 % in patients with subarachnoid hemorrhage.

### **Magnesium**

The potential neuroprotective mechanisms of magnesium include reduction of the pre-synaptic glutamate release, blockade of NMDA-receptors, improvement of mitochondrial calcium buffering, blockade of calcium entry via voltage-gated channels and relaxation of smooth muscles, which might be beneficial in patients with vasospasm after SAH. An investigation in 110 patients suffering from aneurysmatic subarachnoid hemorrhage tested the potential of magnesium sulphate infusion to prevent secondary ischemic events. There was an overall lower incidence of delayed cerebral vasospasm plus less delayed ischemic infarction in those patients developing vasospasm. Monitoring of constant serum magnesium concentrations between 2.0 and 2.5 mmol/L was unique in this protocol and allows for the conclusion that this regimen is safe provided that neuro intensive care is continuously available.

### **Erythropoietin**

Cerebral erythropoietin is produced in the hippocampus, internal capsule, the cortex, endothelial cells, and astrocytes and its receptors are expressed by neurons, microglia, astrocytes and cerebral endothelial cells. Hypoxia and ischaemia have been recognized as important driving forces of erythropoietin expression in the brain, suggesting that erythropoietin is part of a self-regulating physiological protection mechanism to prevent neuronal injury. Systemic application of the growth factor erythropoietin stimulates neurogenesis, neuronal differentiation, and activates brain neurotrophic, anti-apoptotic, antioxidant, and anti-inflammatory signaling. These multiple protective approaches were confirmed in animal models of focal and global cerebral infarction and of traumatic brain injury. A single center study has investigated 80 patients with aneurysmatic subarachnoid haemorrhage. In these patients 90,000 IU of erythropoietin seemed to decrease the severity of vasospasm and shortening of impaired autoregulation along with a reduction of delayed cerebral ischemia.

### **Statins**

Statins (3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors) are indicated in patients suffering from hypercholesterolemia as they reduce morbidity and mortality from adverse cardiac events, stroke, and peripheral vascular disease. However, statins promote other effects that are independent of changes in serum cholesterol. These “pleiotropic” effects include attenuation of vascular inflammation, improved endothelial cell function, stabilization of atherosclerotic plaque, decreased vascular smooth muscle cell migration and proliferation, and inhibition of platelet aggregation. Meta-anal-

yses investigating the efficacy of statin treatment in patients with aneurysmal subarachnoid hemorrhage reported conflicting results. One systematic review including 3 randomized, placebo-controlled trials revealed a reduced incidence of vasospasm, delayed cerebral ischemia, and mortality in statin-treated patients but was criticized for its methodology. The latest meta-analysis including 4 trials did not lend statistically significant support to the finding of a beneficial effect of statins in patients with aneurysmal subarachnoid hemorrhage. The conflict of these two systematic reviews may relate to differences in the philosophy of the analyses: the authors should not test for the null hypothesis at the 5 % level rather than address the size of treatment and direction of effect as well as the precision of estimate (width of CI). Because of the above differences in approach of interpretation, both trials may be “close to the truth”. As a consequence, the use of statins in treating vasospasm and delayed ischemic neurological deficits as the only target cannot be recommended at this time.

### **Glucocorticoids**

The proposed mechanisms by which glucocorticoids reduce neuronal injury include increased order of lipid bilayers, free radical scavenging, and prevention of free fatty acid-accumulation by inhibition of lipidperoxidation. Studies in patients with acute stroke or following cardiac arrest could not demonstrate a significant reduction in infarct size or improvement in neurologic outcome with the infusion of glucocorticoids (e. g. dexamethasone or methylprednisolon) despite some positive effects in experimental preparations. Likewise, controlled clinical trials were unable to detect improved outcome in patients with head injury receiving either dexamethasone or methylprednisolone. Three subarachnoid hemorrhage trials with 256 randomised patients were analyzed by the Cochrane Collaboration. There were major differences in study populations and drugs, as well as methodological quality. Patients were treated with hydrocortisone or fludrocortisone acetate but the overall low number of patients and the wide confidence intervals did not clarify the balance between beneficial or adverse effects of corticosteroids in patients with SAH.

### **Hypothermia**

Interest in thermal interventions is related to the characteristic cerebral effects of moderate (29–32 °C) and mild hypothermia (33–36 °C) since observations in laboratory animals and humans have shown neuronal protection. Small reductions in brain temperature during increased ICP and cerebral ischemia. Hypothermic protection is related to suppression of major biochemical processes such as decreases in cerebral metabolism, reduction of excitatory neurotransmitter release, and inhibition of accumulation of lipid peroxidation products and free radical generation. Other studies indicate that small changes in temperature economize CBF and prevent postischemic hyper- and hypoperfusion and formation of brain edema. Unfortunately, a randomized controlled trial on intraoperative hypothermia during surgical clipping of intracranial aneurysms was unable to demonstrate differences in neurologic outcome. Thus, therapeutic cooling is not justified in these patients

### **Conclusion**

The plethora of perioperative pathophysiological events in patients scheduled for intracranial aneurysm surgery requires a holistic medical approach. It is essential to maintain homeostasis by controlling for normotension, normovolemia, normoxia, normocapnia, normothermia and normoglycemia. Additionally, the use of oral nimodipine is indicated, There is inadequate evidence for the treatment with magnesium and statins. Erythropoietin, steroids, triple-H and intraoperative hypothermia are not indicated.

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