Management of physiological variables in neuroanaesthesia: maintaining homeostasis during intracranial surgery

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Purpose of review
The recent literature on the perioperative maintenance of cerebral homeostasis was reviewed.

Recent findings
Several studies focused on the regulation of cerebral blood flow in patients without intracranial disease; therefore, further studies in neurosurgical patients are needed. High intracranial pressure and brain swelling can be controlled by the choice of anaesthetic agents, and also by optimal positioning of the patient. The use of positive end-expiratory pressure may impair cerebral blood flow, but the effects of positive end-expiratory pressure seem to depend on the respiratory system compliance. The international multicenter study failed to show any benefit from intraoperative hypothermia in patients with subarachnoid hemorrhage; similarly, the results on corticosteroid therapy in head-injured patients are discouraging. Corticosteroid therapy has prompted studies on the control of blood glucose levels. While tight glycemic control has been recommended, it can have untoward effects manifested as cerebral metabolic stress.

Summary
From the clinical point of view, the recent research has added only little to the knowledge on the management of physiological parameters in neurosurgery. More adequately powered studies focusing in specific problems, and having a meaningful aim relative to outcome, are needed also in neuroanaesthesia.

Keywords
autoregulation, blood glucose, cerebral blood flow, hypothermia, intracranial pressure, ventilation

Abbreviations

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<tr>
<td>CBF</td>
<td>cerebral blood flow</td>
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<td>CPP</td>
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<td>central venous pressure</td>
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<td>MAP</td>
<td>mean arterial pressure</td>
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Introduction
The most important aims of neuroanaesthesia are, first, to provide adequate cerebral perfusion pressure (CPP) and blood flow (CBF) to meet the tissue demands of oxygen and glucose and, second, on the occasion of a decreased supply, to protect the brain.

To achieve and maintain the homeostasis, it is essential to understand not only the regulation of the CBF in a healthy brain and during a number of pathological states, but also to know the effects of the anaesthetic agents on it. After the opening of the dura, the intracranial pressure (ICP) is virtually zero, but the swelling of the brain can impair the working conditions of the neurosurgeon. The effects of various factors on the ICP must be considered during the induction of anaesthesia and again after the dura is closed.

Fast emergence after craniotomy has been considered of importance, because immediate neurological examination is desirable to reveal such new deficiencies that may need an intervention. The most commonly used anaesthetic regimens – propofol–remifentanil or sevoflurane–fentanyl – seem to be equal in terms of emergence time and the return of early cognitive function [1].

In this article, we have reviewed the recent publications on the management of the essential physiological parameters in neuroanaesthesia, and the effects of anesthetic agents are discussed.

CPP, CBF and autoregulation
In the healthy brain, the cerebral blood flow (CBF) is well regulated to meet the demands for oxygen and glucose, but the cerebrovascular autoregulation can be disturbed by various pathological states and also by anaesthetic agents. With intact autoregulation, the CBF remains constant within a wide range of CPP and, with abrupt changes in...
the arterial pressure and consequently in the CPP, dynamic autoregulation restores the CBF to the normal level. Traditionally, CPP has been calculated as mean arterial pressure (MAP) – ICP, but recent studies [2] suggest that this formula is valid only if ICP is high and, in subjects without increased ICP, the major determinant of the effective downstream pressure is the vascular tone. The formula to calculate the CPP in the latter case is MAP – ZFP, in which ZFP (zero flow pressure) represents the MAP at which the blood flow through the cerebral vasculature would cease. Marval and co-workers [3] showed in 23 healthy subjects that during propofol anaesthesia, MAP and the estimated CPP decreased while during sevoflurane anaesthesia estimated CPP was maintained close to the baseline value. Accordingly, the ZFP increased in the propofol group and decreased in the sevoflurane group during normocapnia. Similarly, nitrous oxide – a cerebrovascular vasodilator – increased the estimated CPP and decreased the ZFP in healthy volunteers [4]. These results apply only in patients with normal ICPs; in most neurosurgical patients, however, ICP is increased from the normal level, or the compensatory mechanisms to maintain normal ICP can be close to exhaustion, with the risk of sudden increases in the ICP with only minor changes in the intracranial blood volume.

It has been reported [5] earlier that hyperventilation can restore impaired autoregulation in patients with various diseases and that volatile anaesthetic agents disturb autoregulation in a dose-dependent fashion. In healthy patients anaesthetized with isoflurane first in a dose causing electrical silence in the EEG and the dose reduced thereafter to 0.1–0.2% less than required for EEG silence, autoregulation was disturbed in eight of 12 subjects during normocapnia, and in none during hypocapnia. The authors call for further studies to confirm the effect in neurosurgical patients. With sevoflurane, 1.0–1.2% end-tidal concentration (less than 1 MAC), cerebral autoregulation was virtually intact in normoventilated healthy patients [6]. The results emphasize the differences between volatile anaesthetics and the effects of different depths of anaesthesia. In the same setting, carbon dioxide reactivity was similar in the middle cerebral and basilar arteries. Also, cerebrovascular autoregulation was maintained during stellate ganglion block that increased the estimated CPP and decreased the ZFP. The effect was considered to be due to a decrease in the cerebral vascular tone, similar to what is seen with the volatile anaesthetics [7].

The changes in the regional CBF have been studied [8,9] with PET (positron emission tomography) to elucidate the sites of action of the anaesthetic drugs. In healthy volunteers, neither subanaesthetic nor anaesthetic doses of sevoflurane changed the global CBF. The most significant changes were observed in areas related to pain processing, and with 0.7 and 2.0% end-tidal concentrations, there was a decrease in the regional CBF in the thalamus [9]. In another study [8], comparing sevoflurane at 1, 1.5 and 2 MAC or propofol at EC50 in healthy volunteers, a reduction of global CBF was seen in both groups, but more so in the subjects who received propofol. On the contrary, S-ketamine increases the whole-brain CBF in excess of the metabolic needs [10]. The changes in the CBF, and consequently in the intracranial blood volume, need to be considered in patients with high ICP and a risk for brain swelling during surgery.

ICP and brain swelling

Controlling the high ICP, or preventing any further increases in the ICP, are essential during the anaesthesia induction, to avoid even short periods of insufficient perfusion pressure followed by a secondary injury to the brain and to improve the working conditions for the neurosurgeon. Also, after the opening of the dura, attempts to prevent and reduce brain swelling are often necessary during neurosurgery. On most occasions, the ICP is not known when anaesthesia is induced; therefore, it is mandatory to recognize all the factors that have an effect on it. Cold and his coworkers [9] routinely insert a subdural cannula through the first burr hole at the beginning of craniotomy, to measure the ICP, and the changes in it caused by any chosen variable. In a prospective study [11] of close to 700 patients undergoing craniotomy for supratentorial brain tumors, the independent risk factors of intraoperative brain swelling were subdural ICP measured at the start of surgery, the degree of midline shift and a histopathological diagnosis of either glioblastoma or a metastasis. At an ICP of greater than 13 mmHg, brain swelling was highly probable.

The ICP was higher and the brain swelling was more pronounced in the prone compared with the supine position in children with space occupying intracranial tumors [12]. In patients with subarachnoid hemorrhage (SAH), reverse 10° Trendelenburg position decreased the ICP in 25 of 28 patients, regardless of the anaesthetic agents used (propofol with either fentanyl or remifentanil), whereas the CPP remained unchanged. Also, the dural tension, subjectively evaluated by the neurosurgeon, decreased significantly after the positioning [13]. A cine phase-contrast magnetic resonance imaging (MRI) study [14] in healthy volunteers suggests that the better cerebrovascular and intracranial compliance in the sitting position compared with the supine position can be a result of reduced amount of intracranial blood and cerebrospinal fluid.

The drugs used for the induction and the maintenance of anaesthesia were not identified as independent risk factors for increases in ICP or dural tension or the occurrence of brain swelling during craniotomy [11]. In patients with...
impaired autoregulation of the cerebral circulation, an increase in the arterial pressure as a response to a painful stimulus can be followed by an increase in the ICP, as shown in patients undergoing a ventriculoperitoneal shunt insertion [15]. When alfentanil as a bolus (10, 20 or 30 \( \mu \)g kg\(^{-1}\)) followed by an infusion (10, 20 or 30 \( \mu \)g kg\(^{-1}\) h\(^{-1}\), respectively) was added to fentanyl and propofol anaesthesia, no changes in ICP or brain swelling were noted in the study groups, or when compared with a control group without alfentanil, although CPP decreased in patients who received alfentanil [16*]. The group sizes were small; there were 31 patients included in the study, but the results suggest that administration of alfentanil is well tolerated in neurosurgical patients.

Smith and others [17**] studied the effects of desflurane and isoflurane, at age-corrected 1 MAC, and propofol on the CBF velocity in children presenting for general surgery. When propofol was changed to desflurane, the middle cerebral artery flow velocity increased, but when the volatile anaesthetics were interchanged, there were no changes in the blood flow velocity. In adults, in doses to produce similar depth of anaesthesia, the vasodilating effect was significantly greater with desflurane than isoflurane [18*]. These data suggest that due to the more pronounced vasodilatory effect in the cerebral vasculature, desflurane is less suitable for neuroanaesthesia than isoflurane.

Indomethacin is a known cerebral vasoconstrictor and the feasibility of the drug has been recently discussed in a review by Rasmussen [19**]. Clinical and experimental evidence exists of indomethacin’s vasoconstrictive effect being mainly at the resistance vessels and indomethacin does not affect normal autoregulation. The decrease in CBF is not secondary to a reduction in cerebral glucose metabolism. Furthermore, indomethacin is not likely to cause cerebral ischaemia, and it may even be neuroprotective. In a study [20] of patients with supratentorial tumors, after a bolus of indomethacin 0.2 mg kg\(^{-1}\), an infusion 0.2 mg kg\(^{-1}\) h\(^{-1}\) was started before the anaesthesia induction with propofol, and terminated after the opening of the dura. While indomethacin decreased the CBF velocity before the induction of anaesthesia, indomethacin was not shown to decrease the ICP. These results were explained by propofol-induced vasoconstriction, and that indomethacin did not cause any further change in the blood vessel caliber. Furthermore, hyperventilation does not result in additional cerebrovascular vasoconstriction and subsequent reduction in the ICP in patients administered propofol and indomethacin.

**Tissue oxygenation and oxygen supply (Hb)**

Various physiological changes can affect brain oxygenation, as measured regionally by near infrared spectroscopy or globally by jugular bulb oxygen saturation. In hip arthroplasty patients anaesthetized either by propofol or sevoflurane in oxygen and nitrous oxide, haemodilution to haemoglobin concentration of 80 g/L resulted in a parallel reduction in the regional oxygen saturation, but not in the jugular bulb oxygen saturation [21]. The adequate Hb in neurosurgical patients during craniotomy remains to be elucidated.

The decrease in MAP during anaesthesia induction with propofol caused minimal changes in the regional oxygen saturation in young and elderly patients, and the changes were related to those in MAP [22].

**Temperature**

Thome et al. [23*] reviewed the pathophysiological basis of the neuroprotective effects of hypothermia in acute and chronic phase of SAH. In the clinical setting, few studies exist about its benefits in SAH patients, calling for more prospective controlled studies.

The effect of induced hypothermia on outcome of 1001 SAH patients undergoing neurovascular surgery was studied in a large international multicenter study – IHAST (the Intraoperative Hypothermia for Aneurysm Surgery Trial) [24**]. In the normothermia group, body temperature was kept between 36 and 37°C and, in the hypothermia group, the target temperature was between 32.5 and 33.5°C. Rewarming was started after the last clip had been secured. The study could not show any beneficial effects associated with intraoperative hypothermia. At the follow-up, 90 days after surgery, 66% of patients in the hypothermia group and 63% of patients in the normothermia group were classified as having good outcome (Glasgow outcome scale 1). There were no differences between the groups with respect to postoperative adverse events, with the exception of bacteremia, which occurred more often in the hypothermia group. The limitations of this study were the relatively short time for cooling, the uncontrolled postoperative care and the ‘crude’ tool used for outcome assessment. Until so far, there is no evidence that induced intraoperative hypothermia improves the outcome of SAH patients.

**Ventilation strategy and cerebro–pulmonary interactions**

Patients with acute head injury or SAH often suffer from respiratory failure caused by neurogenic pulmonary edema and acute lung injury. This pathological process may even result in the development of cardiogenic shock [25]. Acute lung injury has recently been reported [26] to occur in 27% of SAH patients and is associated with increased hospital mortality. The treatment of respiratory failure should be aggressive and mechanical ventilation should be started early enough, because hypoxia and hypercarbia may worsen the secondary brain injury. Positive end-expiratory pressure (PEEP) ventilation is
generally used to maintain adequate oxygenation. This treatment may have deleterious effects on CBF and ICP by causing hypotension and thus decreasing CPP and resulting in a decrease in brain oxygen delivery and in cerebral ischemia. As patients with simultaneous intracerebral and lung injury undergo surgical interventions, it is also important to know the potential adverse effects of anesthetic agents on vascular permeability in lung.

Muench and co-workers [27] studied the effects of various PEEP levels on ICP, brain tissue oxygen tension, regional CBF and haemodynamic variables. In the experimental part, in healthy pigs, elevation of PEEP up to 25 cmH₂O did not have adverse effects in ICP, brain tissue oxygen tension or regional CBF, although the central venous pressure (CVP) increased. Arterial oxygenation improved and carbon dioxide values increased. In the clinical part of the study, elevation of PEEP up to 20 cmH₂O did not affect arterial oxygenation, carbon dioxide or cardiac index but increased CVP in patients with SAH. Changes in ICP, however, were only moderate. The elevation of PEEP resulted in significant decrease of MAP and regional CBF, indicating disturbed cerebral autoregulation. Normalization of MAP restored regional CBF. The study suggests that maintenance of MAP is the most important factor to ensure sufficient cerebral oxygenation. A limitation of the study was that the study patients did not have lung injury, and required mechanical ventilation due to neurological deficits.

Caricato and co-workers [28] investigated the intracranial effects of PEEP in 21 comatose patients, eight of whom had low respiratory system compliance. In patients with normal respiratory system compliance, incremental PEEP increased CVP and decreased MAP and CPP and in patients with low respiratory system compliance, elevation of PEEP up to 12 mmHg did not influence MAP or CPP. On average, ICP did not change in either group. The variations in ICP were unpredictable, however, as ICP increased in 38% of all study patients. The respiratory system compliance may be one of the main factors affecting the transmission of PEEP to the intracranial system. Therefore, the authors recommend measurement of respiratory system compliance to identify patients with a risk for harmful effects of PEEP on the intracranial system.

PEEP, however, may also affect cerebral circulation by CO₂-mediated mechanisms. Twelve patients with brain injury and severe acute lung injury were divided into recruiters and nonrecruiters according to the effects of PEEP on volume-pressure curves of the respiratory system. In recruiters, elastance of the respiratory system decreased and PaCO₂, ICP, mean Vmca and SjO₂ remained stable after application of PEEP, while in nonrecruiters, elastance increased as did also PaCO₂, ICP, mean Vmca and SjO₂. The authors concluded that effects of PEEP on cerebral hemodynamics depend on the recruitment of alveolar units and PaCO₂ variations [29]. Thus, it seems that the effects of PEEP on ICP in head injury or SAH patients with concomitant lung depend on various factors, and monitoring both cerebral perfusion and ICP and lung mechanics in patients with simultaneous central nervous and respiratory system damage is advisable. As the studies so far show somewhat conflicting results, more clinical studies to clarify this issue are needed.

The effects of anesthetic agents on vascular permeability in lung in the presence of head injury or intracranial hemorrhage are poorly documented. The effects of isoflurane and sevoflurane on the development of neurogenic pulmonary edema were studied in a rat model by exposing the animals to room air, 1.5% isoflurane or 2.5% sevoflurane. Fifty-eight per cent of rats in the control group, 100% of those exposed to isoflurane and 5% of those exposed to sevoflurane developed neurogenic pulmonary edema after the injection of fibrinogen and thrombin into the cisterna magna. In the lungs exposed to isoflurane, immunohistochemical staining of bronchial epithelial cells for vascular endothelial growth factor demonstrated an increased expression. Sevoflurane exposition lacked such harmful effects [30]. The clinical implications of these findings remain to be established.

**Corticosteroid therapy and intraoperative hyperglycemia**

In a recent large international multicenter study – CRASH (corticosteroid randomization after significant head injury) [31,32] – the benefit of corticosteroid therapy has been questioned in head injury patients. Indeed, the risk of death from all causes within 2 weeks was higher in the group receiving corticosteroid treatment (21.1%) than in the placebo group (17.9%) [31]. The risk of death remained elevated also at 6 months [32]. The reasons for increased mortality in this study constituting 10 008 randomized patients, however, remained unclear. It has been speculated, that one factor modifying the findings of the CRASH trial may be hyperglycemia caused by corticosteroid therapy [33].

Lukins and Manninen [34] conducted a prospective nonrandomized study about the association of dexamethasone therapy and blood glucose levels among nondiabetic patients undergoing craniotomy. The study showed that patients who received dexamethasone before, during and after surgery had significantly higher peak glucose concentrations (11.0 ± 2.0 mmol/l) than those receiving it during and after surgery (8.5 ± 1.2 mmol/l) or those who did not receive
Convincing evidence that tight glycemic control has beneficial effects in critically ill and in cardiac surgical patients exists [36] and early hyperglycemia was associated with poor outcomes in patients with head injury [37], and insulin treatment appeared well tolerated and feasible in SAH patients [38]. In a retrospective analysis of data [39] from 47 traumatic brain injury (TBI) patients, however, intensive insulin therapy was associated with signs of cellular distress, as indicated by changes in microdialysis markers. Whether tight glycemic control improves outcome in patients undergoing neurosurgical operations remains to be found out in further randomized and controlled studies.

Conclusions

Several studies on the effects of various factors on cerebral circulation in healthy subjects exist, but the results are to be interpreted cautiously in the neuroanaesthesia context. The untoward increases in ICP and intraoperative brain swelling can be controlled with careful positioning but also by pharmacological means. Two multicenter studies showed discouraging results: intraoperative hypothermia does not benefit the SAH patients, and the value of corticosteroid therapy in head injury patients has been questioned.

From the clinical point of view, the recent research has added only little to the knowledge on the management of physiological parameters in neurosurgical patients. More adequately powered studies focusing in specific problems, and having a meaningful aim relative to outcome, are needed also in neuroanaesthesia.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 579–580).


11. The PET study in healthy volunteers showed an increase in CBF after S-ketamine administration.


15. The PET study in healthy volunteers showed an increase in CBF after S-ketamine administration.


18. The PET study in healthy volunteers showed an increase in CBF after S-ketamine administration.


22. The PET study in healthy volunteers showed an increase in CBF after S-ketamine administration.


26. The PET study in healthy volunteers showed an increase in CBF after S-ketamine administration.
In patients undergoing supratentorial craniotomy, three different doses of alfentanil were not noted. Haemodynamic changes during the tunneling phase of ventriculoperitoneal shunt insertion, tunneling was followed by a significant increase in the MAP, and consequently in the ICP.

In patients undergoing ventriculoperitoneal shunt insertion, tunneling was made from desflurane to propofol. With isoflurane–propofol, similar changes were not noted. When propofol is changed to desflurane, but not when isoflurane is changed to desflurane in children. Accordingly, Vmca decreased when the change was made from desflurane to propofol. With isoflurane–propofol, similar changes were not noted.

At the similar anaesthetic depth, desflurane caused more vasodilation than isoflurane, as measured by Vmca.

This is a comprehensive review of the use of indomethacin in neurosurgical patients. The mechanisms of action and the effects on cerebral blood flow and ICP as well as the possible other effects are discussed. The effects of PEEP are studied in an animal model and a series of SAH patients without lung injury.

An experimental study about the effects of isoflurane and sevoflurane on lung vascular permeability. Isoflurane predisposed to the development of neurogenic pulmonary edema in an animal model.


A large multicenter study, containing 10 008 randomized patients, strongly questions the use of corticosteroids in head trauma.

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