



Anesthesiology Clin N Am
20 (2002) 315–327

ANESTHESIOLOGY
CLINICS OF
NORTH AMERICA

Brain protection during neurosurgery

Verna L. Baughman, MD

*Division of Neuroanesthesiology, Departments of Anesthesiology and Neurosurgery,
University of Illinois at Chicago, Suite 3200, 1740 W. Taylor Street (M/C 515),
Chicago, IL 60612, USA*

Protecting the brain from ischemia during neurosurgery is one of the most important concerns for anesthesiologists. It is amazing that, to my knowledge, there is a paucity of prospective randomized controlled clinical trials comparing different treatments upon which to base cerebral protectant therapy. However, there is a wealth of laboratory research, both *in vivo* and *in vitro*, which supply the neuroanesthesiologist with theories that guide the management of patients at risk for cerebral ischemia.

There are three major themes to this chapter. The first section reviews the research that led to the establishment of barbiturates as the gold standard for cerebral protection. The second discusses current methods of providing intra-operative cerebral protection. The third examines new and exciting possibilities regarding therapy/drugs that may become important tools in the future for cerebral protection.

The past: the development of barbiturates as the gold standard for cerebral protection

A brief examination of the historical sequence of barbiturate use for cerebral protection provides insight into not only the choice of this drug category but also the proposed mechanisms of ischemia. The classic theory of cerebral protection is based on the concept that by decreasing cerebral metabolic demand, the neuronal survival will improve during periods of inadequate cerebral blood flow (CBF). Because barbiturates decrease cerebral metabolism, it was the first drug group to be considered as a potential cerebral protectant.

In the 1970s Michenfelder demonstrated that barbiturates decreased cerebral metabolic activity in a dose-dependent manner, which produced a progressive decrease in EEG activity, a reduction in the rate of ATP depletion, and protection

E-mail address: vbaughma@uic.edu (V.L. Baughman).

from incomplete cerebral ischemia [1–3]. Elimination of the metabolic requirement for EEG activity permitted this energy to be available for neuronal basal metabolic needs. Current clinical practices of providing cerebral protection are based on this concept. When the EEG is isoelectric, neuronal energy consumption is decreased by approximately 50%. Therefore, with barbiturate treatment to an isoelectric EEG during ischemia, all metabolic energy is used for maintenance of cellular integrity. Additional barbiturate dosing produces no further reduction in cerebral metabolism.

An early study by Bleyaert [4] supported the use of barbiturates as a cerebral protectant. Using a neck tourniquet to completely eliminate blood flow to the brain, the authors reported good neurologic outcome in barbiturate-pretreated (thiopental, 90 mg/kg) monkeys compared to control animals. However, when Gisvold [5] repeated this experiment he was unable to reproduce the positive results. This difference is probably due not to the drug treatment but rather to the postoperative care. In the first study the barbiturate-treated monkeys remained intubated and ventilated following reperfusion due to the large barbiturate dose, whereas the control animals were extubated early and returned to their cages without additional oxygen or intravenous fluids. In the second study both barbiturate and control animals received similar post-ischemia care. The difference in outcome disappeared when both groups received identical ICU supportive treatment. In both studies EEG activity disappeared with the initiation of complete cerebral ischemia (neck tourniquet inflation), so it is reasonable to conclude that the drug-induced suppression of EEG metabolic activity was immaterial because the EEG was abolished by the study design.

The Brain Resuscitation Clinical Trial [6] confirmed the lack of barbiturate protection in humans following complete absence of CBF. After resuscitation from cardiac arrest patients were randomized to receive either thiopental (30 mg/kg, infusion over time as blood pressure would permit) or saline. Mortality was high in both groups (77% versus 80%). This human experiment confirmed that barbiturates were ineffective in preventing or ameliorating cerebral ischemic damage that occurred in the setting of complete ischemia (ie, no blood flow to the brain). With cessation of CBF, the EEG becomes isoelectric within 1–2 minutes. Therefore, any drug that suppresses EEG activity will be ineffective because the EEG is already isoelectric.

Following up on the theory that barbiturates work only during incomplete ischemia (ie, when EEG activity is still present during the ischemic period), Nussmeier examined the protective potential of barbiturates when CBF was substantially decreased but not completely interrupted [7]. She randomized normothermic cardiac surgery patients to either thiopental 39.5 mg/kg infusion or placebo. Neurologic outcome was improved in thiopental-treated patients having valve replacement operations (in which the left ventricle was open, which presumably resulted in cerebral air emboli with the reestablishment of circulation). Zaidan [8] replicated Neussmeier's study; however, he used hypothermic cardiopulmonary bypass and found no difference between the two groups. The

most logical explanation for the difference in outcome between these two cardiac surgery studies is that the barbiturate protective effect was invisible in the face of the hypothermia treatment.

Summary

The conclusions derived from this research have shaped our clinical approach to cerebral protection. Barbiturates decrease cerebral metabolism in a dose-dependent manner until the EEG becomes isoelectric. Additional drug doses after an isoelectric EEG provide no additional metabolic depression. Barbiturates provide cerebral protection in the face of incomplete ischemia, but not with complete cessation of CBF (complete ischemia). In situations where CBF is completely arrested, EEG activity disappears within 90 seconds, so the administration of a drug to depress EEG metabolic activity would be irrelevant.

The present: current cerebral protection treatments

One would expect any anesthetic that depresses cerebral metabolism and EEG activity to be similar to barbiturates in providing cerebral protection from ischemia. The following section reviews current anesthetic drugs and evaluates their potential for cerebral protection.

Etomidate

Etomidate, an intravenous sedative-hypnotic, is similar to barbiturates in decreasing cerebral metabolism progressively until an isoelectric EEG appears [9]. Unlike barbiturates, etomidate has very little effect on blood pressure, and a short duration of action. For these reasons it was frequently used as a cerebral protectant because it produced approximately 50% reduction in cerebral oxygen demand while preserving cerebral perfusion pressure. Etomidate has demonstrated protection in some laboratory research models [10–12]; however, the results are not universally positive [13,14], suggesting that etomidate might provide protection only during mild to moderate ischemia. In some animal models, etomidate initially decreases CBF to a greater degree than cerebral metabolism, potentially putting the brain at risk of inadequate substrate delivery [15]. It must also be remembered that etomidate produces adrenal depression (inhibition of 11- β -hydroxylase), which caused increased mortality when it was used as a continuous infusion for sedation in the ICU [16]. This inhibition lasts 4–6 hours with a single dose, but is prolonged with continuous infusion or in elderly critically ill patients [17].

Propofol

Propofol, introduced into clinical practice in the late 1980s, depresses cerebral metabolism in a dose dependent manner, similar to barbiturates, producing

isoelectric EEG at clinically relevant doses [18]. Rapid emergence from burst suppression EEG may permit more accurate postanesthesia neurologic evaluation. It has been used to provide brain protection in multiple laboratory studies; however, no clinical studies compare its cerebral protection potency to barbiturates. Because propofol has significant negative inotropic activity in addition to vasodilatory properties, it can decrease cerebral perfusion pressure when a large dose is administered over a short period of time. Propofol has been shown to be superior to fentanyl–nitrous oxide anesthesia in a rat model of incomplete ischemia [19] and equal to halothane in a regional cerebral ischemic rat model [20]. Additionally, propofol may afford cerebral protection by its antioxidant potential [21] or by acting as a glutamate antagonist at the N-methyl-D-aspartate (NMDA) receptor [22].

Opioids

Narcotic-based anesthesia has been a foundation for neuroanesthesia because opioids have little effect on cerebral metabolism and blood flow while supporting the cardiovascular system and cerebral perfusion pressure. Some literature questions the safety of narcotics (increased intracranial pressure—ICP) [23]. These changes are small, and appear to be due to cerebral vasodilation in response to a decrease in blood pressure [24]. Maintenance of blood pressure appears to reduce or eliminate the mild increase in ICP. It has been reported that large doses of opioids can produce seizure activity in animals [25]. However, the wide-spread use of opioids in neuroanesthesia without evidence of seizure activity speaks to the safety of this class of drugs. Evidence as to whether opioids produce neuroprotection and the possible mechanism of this action is lacking.

Benzodiazepines

Benzodiazepines also depress cerebral metabolism in a dose-response manner; however, they are not as potent as barbiturates (maximal decrease in cerebral metabolism is 25–30%), and do not produce isoelectricity [13,26]. Because they are unable to maximally suppress EEG activity, they have not been seriously considered for cerebral protection.

Ketamine

Ketamine is a controversial drug in neuroanesthesia because it has been shown to increase both cerebral metabolism and blood flow [27]. Animal studies regarding the effectiveness of ketamine as a cerebral protectant are both supportive [28,29] and contradictory [30]. Recently, however, ketamine has been proposed as an anesthetic drug that may provide cerebral protection because it blocks the NMDA receptor, which is highly activated via enhanced excitatory neurotransmitter release during ischemia [31]. In vitro studies show ketamine can also interfere with transmembrane calcium influx [32]. Initial concern that ketamine

increases intracranial pressure in spontaneously breathing subjects has been eliminated by demonstrating no increase in pressure when administered to anesthetized, ventilated patients [33]. Ketamine's place as a neuroprotectant is still debatable.

Nitrous oxide

Nitrous oxide has been used in neuroanesthesia for many years. Its rapid on/off action makes it a useful addition to the anesthetic plan. Despite its track record, nitrous oxide possesses undesirable characteristics. Nitrous oxide increases CBF, which could cause problems in patients with increased intracranial pressure [34,35]. When used alone, nitrous oxide can increase CBF by 37% and cerebral metabolism [36]. When used in combination with inhalational anesthetics, the CBF increase persists, but to a lesser degree [37]. Whether these vascular effects translate into ischemic injury is debatable, with some animal data demonstrating worse outcome [38] while other studies show no effect [39]. Because it readily diffuses into air containing spaces, and because pneumocephalus is evident in computerized tomography (CT scans) for up to 2 weeks postcraniotomy, nitrous oxide should not be used during this time frame. Whether or not the use of nitrous oxide is harmful has not been established in clinical studies.

Inhalation anesthetics

Almost all of the inhalational anesthetic agents are similar to barbiturates in producing progressive EEG depression in a dose-dependent manner until obtaining electrical silence. This occurs at approximately 1.5–2 MAC. Concurrent with EEG suppression is a reduction in cerebral metabolism by approximately 50% when the EEG is isoelectric. Because of this similarity to barbiturates, inhalational anesthetics are frequently used for cerebral protection. They produce less cardiovascular depression than the barbiturates, and are more rapidly eliminated at the end of surgery. The exceptions are halothane and enflurane. Halothane requires about 4 MAC for isoelectricity, which is clinically impractical. Halothane also increases intracranial pressure by cerebral vasodilation unless hyperventilation is initiated prior to the introduction of halothane. Enflurane has been reported to produce seizure like activity on EEG, especially when paired with hyperventilation.

Are there differences among the inhalational anesthetics in brain protection? Laboratory and clinical studies suggest that they all provide cerebral protection, but a direct comparison among all of the agents is lacking. Are they as good or better than barbiturates? Multiple experiments have compared inhalational anesthetics to barbiturates and other intravenous drugs. The results are variable. A comparison between desflurane and thiopental in neurosurgical patients showed an increase in brain oxygen (using a brain probe) with desflurane when both were administered to EEG burst suppression [40]. Blood pressure

was supported to maintain adequate CBF due to a loss of autoregulation. Are these results drug specific or do they reflect the cerebral vascular effects of these drug categories? A recent isoflurane study reported on its ability to modulate release of excitatory neurotransmitters and delay apoptosis (programmed cell death), which may provide a window of opportunity for the administration of other protective agents [41]. Detailed neuropsychiatric outcome studies are needed to determine if there is a difference in neuroprotection among the inhalational agents.

Temperature

The beneficial effect of hypothermia is well known. Hypothermia has long been used during cardiopulmonary bypass and circulatory arrest surgery to provide protection from cerebral ischemia. Initially it was felt that hypothermic protection was based on a significant decrease in cerebral metabolism, allowing the neurons to exist in almost a suspended energy consumption state. However, it has subsequently been shown that profound hypothermia is not required to protect the brain. Even mild levels have proven to be protective [42–44]. For example, with rat global ischemia studies, marked hippocampal injury was seen in 100% of rat brains following 20 minutes of ischemia when tested at 36°C. The injury decreased to 20% when studied at 34°C and 0% at 33°C [45]. This protective effect, which has been reproduced by many investigators, cannot be explained by changes in energy consumption during ischemia. For every degree Centigrade decrease in temperature, cerebral metabolism is reduced by 5–7%. Therefore, a reduction in temperature from 37°C to 34°C produces a 15–20% reduction in cerebral metabolism, which is far less than the 50% decrease seen with EEG silence. Obviously hypothermia's protective effect is not mediated solely by metabolic depression. Proposed mechanisms include suppression of glutamate release [46,47], blunted nitric oxide production [48] which is involved in producing oxygen free radicals, formation of free fatty acids [46], reduced calcium influx [49], and increased gamma-aminobutyric acid (GABA) release during ischemia. Glutamate release is increased 10-fold when temperature is increased to 39°C during ischemia [45,50].

Unfortunately, intraoperative cerebral temperature is usually not monitored. Instead, temperature is measured with esophageal, bladder, rectal, or tympanic membrane probes. Even pulmonary artery catheter measurement may not be reflective of cerebral temperature. To compound this problem, brain temperature during surgery varies from cortical surface to deep intracerebral. It is frustrating that a brain protectant therapy with few side effects is so difficult to correctly implement because of our inability to measure the temperature of the brain region at risk for ischemia. If this were possible, the local cooling methodologies could be used instead of subjecting the entire body to hypothermia. Currently, a multicenter study evaluating the effect of normothermic or mild hypothermic management during cerebral aneurysmal clipping is underway [51]. This is the first time that a study sufficiently large enough to

evaluate a single intraoperative manipulation on neurologic outcome in humans has been initiated.

Blood pressure

Control of blood pressure is possibly one of the most important aspects of preventing brain injury and promoting cerebral protection. The direction and extent of this control depends on the surgical procedure. For example, if aneurysm clipping includes trapping the aneurysm, maintenance of normal or slightly increased blood pressure is indicated to increase collateral perfusion to the area of brain transiently robbed of its blood supply due to the temporary clip. Conversely, a reduction of blood pressure during direct aneurysm clipping may reduce the intra-aneurysm pressure and decrease its potential for rupture during surgical manipulation. Similarly, maintenance or increasing blood pressure during carotid endarterectomy or the anastomosis of an extracranial-intracranial (ECIC) bypass may also improve collateral perfusion to the tissue bed distal to the occluded cerebral blood vessel. The effectiveness of these manipulations depends on the state of vascular patency. For example, if the angiogram shows a complete Circle of Willis, then increasing blood pressure during carotid endarterectomy is appropriate; on the other hand, if the flow through the carotid artery is minimal or the surgeon places a shunt, blood pressure need not be elevated. Increasing blood pressure risks producing myocardial ischemia or vasogenic edema in previously poorly perfused brain tissue because these vessels are not governed by cerebral pressure autoregulation.

The amount and direction of blood pressure control depends upon knowledge of the preoperative flow pattern (it is essential to review the angiogram preoperatively) and the surgical approach, rather than a cookbook methodology. Postoperative management also requires a consideration of the surgical procedure.

Glucose

Serum glucose concentration at the time of ischemia contributes substantially to the ischemic injury. The deleterious effects of hyperglycemia have been well reported in both clinical and laboratory reports [52,53]. Hyperglycemia markedly increases damage in both global and focal ischemia [54,55]. Even moderately elevated serum glucose worsens outcome. During incomplete ischemia the continuous delivery of glucose with an inadequate oxygen supply converts aerobic to anaerobic metabolism, increasing brain lactic acid, which decreases brain pH. Buffering capacity is overwhelmed, free oxygen radicals are generated, neuronal pH decreases, and cell membrane rupture occurs, producing tissue necrosis [56].

There are several specific situations where elevated glucose concentrations may be beneficial. First, in a rat model of cardiac arrest, administration of glucose *plus insulin* (to moderate hyperglycemia) improved functional and histologic outcome [57]. Second, abrupt normalization of hyperglycemia in patients with chronically elevated glucose worsens ischemic damage.

The future

The concept of providing cerebral protection in the future will probably not focus on decreasing cerebral metabolism, but rather on blocking the cascade of events that occur during ischemia (see boxed text).

Potential cerebral protective mechanisms

- Decrease cerebral metabolism
- Increase cerebral blood flow
- Mild hypothermia
- Prevent hyperthermia
- Maintain normoglycemia
- Inhibit release of excitatory neurotransmitters (eg, glutamate, aspartate)
- Enhance release of inhibitory neurotransmitters (eg, GABA)
- Block neuronal calcium influx
- Decrease nitric oxide formation
- Decrease Neuronal free radical formation
- Prevent apoptosis
- Scavenge free radicals
- Prevent Ca^{++} and Na^{+} influx

The ischemic cascade

During cerebral ischemia large amounts of excitatory neurotransmitters (glutamate and aspartate) are released by presynaptic neurons. The amount released correlates with the severity of the ischemic insult and subsequent neuronal damage. Glutamate and aspartate activate postsynaptic receptors (NMDA, amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid [AMPA], kainate), resulting in an increase in intracellular calcium and stimulation of enzyme systems that produce ischemic damage and ultimately neuronal death. Nitric oxide synthase is stimulated, producing large amounts of neuronal nitric oxide. Lipid peroxidases, proteases, and phospholipases are activated, increasing intracellular free fatty acids and free radicals. Capsase, translocase, and endonuclease activity results in DNA fragmentation. Cell membranes become permeable, leading to edema and additional calcium influx. ATP stores are depleted, energy-dependent membrane pumps fail, and neuronal death occurs.

New concepts

Current philosophies of cerebral protection are focusing on these excitatory neurotransmitters and their receptors with the hopes of finding ways to interrupt the cascade of neuronal damage. This section briefly outlines some of the areas and drugs under consideration and currently being evaluated (see boxed text).

Some of the drugs that block glutamate release include inhalation anesthetics (70% reduction), adenosine A1 blockers, and α 2 agonists. Inhalational anesthetics may also increase reuptake of neurotransmitters from the synaptic space. Drugs that competitively block postsynaptic receptors include barbiturates (primarily AMPA and kainate receptors) and possibly inhalation anesthetics. Noncompetitive receptor antagonists include MK801 (dizoclipine), phencyclidine, dextromethorphan, ketamine, and magnesium. Recently, sodium channel inhibition has been reported to decrease both potassium-evoked and spontaneous glutamate release.

Methods to block the ischemic cascade

- Inhibit glutamate release
 - Inhalational anesthetics
 - Adenosine A1 receptor blockers
 - α 2 agonists
 - Hypothermia
 - Sodium channel inhibitors
 - Lamotrigen
 - Etomidate
- NMDA, AMPA, and kainate receptor blockers
 - Barbiturates (mainly AMPA, Kainate)
 - ? Inhalational anesthetics
- Noncompetitive receptor blockers
 - Dizoclipine (MK801)
 - Phencyclidine
 - Dextromethorphan
 - Ketamine
 - Magnesium
 - Propofol
- Block calcium influx
 - Propofol
 - Ketamine
 - Inhalational anesthetics
 - Lidocaine
 - Hypothermia
- Prevent apoptosis
 - Isoflurane
 - Halothane
- Inhibit lipid peroxidation
 - Lazariods (21 aminosteroids)
 - Hypothermia
- Reduce inflammatory cytokines
 - Statins
 - Anti-inflammatory drugs

Estrogen
Heparin
Decrease free radicals
Mannitol
Statins
Hypothermia

Examples of other interesting approaches include aspirin, statins, and free radical scavengers. Aspirin has shown laboratory evidence of neuronal protection (delay in energy depletion and functional recovery), probably due to its antiinflammatory action [58]. Development of COX-2 inhibitors may make this approach feasible. Recent work suggests that the statins, in addition to decreasing atheromatous plaque, may also possess beneficial effects during ischemic stroke and reperfusion [59]. The proposed mechanisms include upregulation of endothelial nitric oxide synthase (which promotes vasodilation) while inhibiting inducible nitric oxide synthase (which increases ischemic damage). They also attenuate the inflammatory cytokine response to ischemia, possess antioxidant properties, and reduce ischemic oxidative stress.

Drugs that decrease free radical formation or enhance free radical scavenging are currently being evaluated as cerebral protectants. These include many well-known drugs such as mannitol and steroids in addition to some new ones. Although laboratory studies are promising, the human studies have not been very encouraging. Because cerebral ischemia is a complex event, a multifocal approach will probably be necessary, focusing at different steps in the pathway of ischemia.

Outlook

The future for developing methodologies to protect the brain from ischemia is bright. The scope and range of potential interventions appears unending. As understanding of the cellular and molecular mechanisms that promote ischemic damage or provide neuronal protection increases, research will become even more exciting. The focus will not be on a single method or drug, but rather a cocktail of options will be used to inhibit the harmful effects of the ischemic cascade.

References

- [1] Michenfelder JD, Milde JH, Sundt TM. Cerebral protection by barbiturate anesthesia. Use of middle cerebral artery occlusion in Java Monkeys. *Arch Neurol* 1976;33:345–50.
- [2] Michenfelder JD, Theye R. Cerebral protection by thiopental during hypoxia. *Anesthesiology* 1973;39:510–7.
- [3] Michenfelder JD. The interdependency of cerebral function and metabolic effects following massive doses of thiopental in the dog. *Anesthesiology* 1974;41:231–6.
- [4] Bleyaert A, Nemoto EM, Safar P, et al. Thiopental amelioration of brain damage after global ischemia in monkeys. *Anesthesiology* 1978;49:390–8.

- [5] Gisvold S, Safar P, Hendrickx HHL, et al. Thiopental treatment after global brain ischemia in pigtailed monkeys. *Anesthesiology* 1984;60:88–96.
- [6] Brain Resuscitation Clinical Trial I Study Group. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. *N Eng J Med* 1986;314:397–403.
- [7] Nussmeier NA, Arlund C, Slogoff S. Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. *Anesthesiology* 1986;64:165–70.
- [8] Zaidan J, Klochany A, Martin WM, et al. Effect of thiopental on neurologic outcome following coronary artery bypass grafting. *Anesthesiology* 1991;74:406–11.
- [9] Milde LN, Milde JH, Michenfelder JD. Cerebral functional, metabolic, and hemodynamic effects of etomidate in dogs. *Anesthesiology* 1985;63:371–7.
- [10] Milde LN, Milde JH. Preservation of cerebral metabolites by etomidate during incomplete cerebral ischemia in dogs. *Anesthesiology* 1986;65:272–7.
- [11] Patel PM, Goskowitz RL, Drummond JC, et al. Etomidate reduces ischemia-induced glutamate release in the hippocampus in rats subjected to incomplete forebrain ischemia. *Anesth Analg* 1995;80:933–9.
- [12] Smith DS, Keykhah MM, O'Neill JJ, et al. The effect of etomidate pretreatment on cerebral high energy metabolites, lactate, and glucose during severe hypoxia in the rat. *Anesthesiology* 1989;71:438–42.
- [13] Baughman VL, Hoffman WE, Miletich DJ, et al. Cerebral metabolic depression and brain protection produced by midazolam and etomidate in the rat. *J Neurosurg Anesthesiol* 1989;1: 22–8.
- [14] Edelman G, Hoffman WE, Charbel FT. Cerebral hypoxia following etomidate administration and temporary cerebral artery occlusion. *Anesth Analg* 1997;85:521–825.
- [15] Frizzell RT, Meyer YJ, Borchers DJ, et al. The effects of etomidate on cerebral metabolism and blood flow in a canine model for hypoperfusion. *J Neurosurg* 1991;74:263–9.
- [16] Fellows IW, Bastow MD, Byrne AJ, et al. Adrenocortical suppression in multiply injured patients: a complication of etomidate treatment. *Fr Med J* 1983;287(6408):1835–7.
- [17] Absalom A, Plodger D, Kong A. Adrenocortical function in critically ill patients 24 hours after a single dose of etomidate. *Anaesthesia* 1999;54:861–7.
- [18] Vandesteene A, Trempont V, Engelman E, et al. Effect of propofol on cerebral blood flow and metabolism in man. *Anaesthesia* 1988;43(Suppl):42–3.
- [19] Kochs E, Hoffman WE, Werner C, et al. The effects of propofol on brain electrical activity, neurologic outcome, and neuronal damage following incomplete ischemia in rats. *Anesthesiology* 1992;76:245–52.
- [20] Ridenour TR, Warner DS, Todd MM, et al. Comparative effects of propofol and halothane on outcome from temporary middle cerebral artery occlusion in the rat. *Anesthesiology* 1992;76: 807–12.
- [21] Murphy PG, Myers DS, Davies MJ, et al. The antioxidant potential of propofol (2,6-diisopropylphenol). *Br J Anaesth* 1992;8:613–8.
- [22] Orser BA, Bertlik M, Wang LY, et al. Inhibition by propofol (2,6 di-isopropylphenol) of the N-methyl-D-aspartate subtype of glutamate receptor in cultured hippocampal neurons. *Br J Pharmacol* 1995;116:1761–8.
- [23] Marx W, Shah N, Long D, et al. Sufentanil, alfentanil, and fentanyl: impact on cerebrospinal fluid pressure in patients with brain tumors. *J Neurosurg Anesthesiol* 1989;1:3–7.
- [24] Werner C, Kochs E, Bause H, et al. Effects of sufentanil on cerebral hemodynamics and intracranial pressure in patients with brain injury. *Anesthesiology* 1995;83:721–6.
- [25] Kofke WA, Garman RH, Tom WC, et al. Alfentanil-induced hypermetabolism, seizure, and histopathology in rat brain. *Anesth Analg* 1992;75:953–64.
- [26] Hoffman WE, Miletich DJ, Albrecht RF. The effects of midazolam on cerebral blood flow and oxygen consumption and its interaction with nitrous oxide. *Anesth Analg* 1986;65:729–33.
- [27] Dawson B, Michenfelder JD, Theye RA. Effect of ketamine on canine cerebral blood flow and metabolism: modification by prior administration of thiopental. *Anesth Analg* 1971;50: 443–7.

- [28] Church J, Zeman S, Lodge D. The neuroprotective effect of ketamine and MK801 after transient cerebral ischemia in rats. *Anesthesiology* 1988;69:702–9.
- [29] Hoffman WE, Pelligrino D, Werner C, et al. Ketamine decreases plasma catecholamines and improves outcome from incomplete cerebral ischemia in rats. *Anesthesiology* 1992;76:755–62.
- [30] Jensen ML, Auer RN. Ketamine fails to protect against ischemia neuronal necrosis in the rat. *Br J Anaesth* 1988;61:206–10.
- [31] Thompson A, et al. An N-methylaspartate receptor-mediated synapse in rat cerebral cortex: a site of action of ketamine? *Nature* 1985;313:479–81.
- [32] Fukuda S, Murakawa T, Takeshita H, et al. Direct effects of ketamine on isolated canine cerebral and mesenteric arteries. *Anesth Analg* 1983;62:553–8.
- [33] Mayberg TS, Lam AM, Matta BF, et al. Ketamine does not increase cerebral blood flow velocity or intracranial pressure during isoflurane/nitrous oxide anesthesia in patients undergoing craniotomy. *Anesth Analg* 1995;81:84–9.
- [34] Henriksen HT, Jorgensen PB. The effect of nitrous oxide on intracranial pressure in patients with intracranial disorders. *Br J Anaesth* 1973;45:486–92.
- [35] Pelligrino DA, Miletich DJ, Hoffman WE, et al. Nitrous oxide markedly increases cerebral cortical metabolic rate and blood flow in the goat. *Anesthesiology* 1984;60:405–12.
- [36] Deutsch G, Samra SA. Effects of nitrous oxide on global and regional cortical blood flow. *Stroke* 1990;21:1293–8.
- [37] Lam AM, Mayberg TS, Eng CC, et al. Nitrous oxide-isoflurane anesthesia causes more cerebral vasodilation than an equipotent dose of isoflurane in humans. *Anesth Analg* 1994;78:462–8.
- [38] Baughman VL, Hoffman WE, Thomas C, et al. The interaction of nitrous oxide and isoflurane with incomplete cerebral ischemia in the rat. *Anesthesiology* 1989;70:767–74.
- [39] Warner DS, Zhou JG, Ramani R, et al. Nitrous oxide does not alter infarct volume in rats undergoing reversible middle cerebral artery occlusion. *Anesthesiology* 1990;73:686–93.
- [40] Hoffman WE, Charbel FT, Edelman G, et al. Thiopental and desflurane for brain protection. *Neurosurgery* 1998;43:1050–3.
- [41] Faberowski LW, Raizada MK, Summers C. Hypoxia- and ischemia-induced neuronal apoptosis is decreased by halothane and isoflurane (Abstract). *J Neurosurg Anesthesiol* 1999;11(4):307.
- [42] Ginsberg MD, Sternau LL, Globus MY, et al. Therapeutic modulation of brain temperature: relevance to ischemic brain injury. *Cerebrovasc Brain Metab Rev* 1992;4(3):189–225.
- [43] Minamisawa H, Nordstrom CH, Smith ML, et al. The influence of mild body and brain hypothermia on ischemic brain damage. *J Cereb Blood Flow Metab* 1990;10(3):365–74.
- [44] Sano T, Drummond JC, Patel PM, et al. A comparison of the cerebral protective effects of isoflurane and mild hypothermia in a model of incomplete forebrain ischemia in the rat. *Anesthesiology* 1992;76:221–8.
- [45] Busto R, Dietrich WD, Globus MY, et al. Small differences in intrischemic brain temperature critically determine the extent of neuronal injury. *J Cereb Blood Flow Metabol* 1987;7:729–38.
- [46] Busto R, Globus MY, Dietrich WD, et al. Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. *Stroke* 1989;20:904–10.
- [47] Patel P, Drummond JC, Cole DJ, et al. Differential temperature sensitivity of ischemia-induced glutamate release and eicosanoid production in rats. *Brain Res* 1994;650:205–11.
- [48] Kader A, Frazzini VI, Baker CJ, et al. Effect of mild hypothermia on nitric oxide synthesis during focal cerebral ischemia. *Neurosurgery* 1994;35:272–7.
- [49] Bickler P, Buck LT, Hansen BM. Effects of isoflurane and hypothermia on glutamate receptor-mediated calcium influx in brain slices. *Anesthesiology* 1994;81:1461–9.
- [50] Takagi E, Ginsberg MD, Globus MY, et al. Effect of hyperthermia on glutamate release in ischemia penumbra after middle cerebral artery occlusion in rats. *Am J Physiol* 1994;266:H1770–6.
- [51] Hindman BJ, Todd MM, Geld AW, et al. Mild hypothermia as a protective therapy during intercranial aneurysm surgery: a randomized prospective pilot trial. *Neurosurgery* 1999;44(1):23–32.
- [52] Longstreth WT Jr, Inui TS. High blood glucose level on hospital admission and poor neurological recovery after cardiac arrest. *Ann Neurol* 1984;15:59–63.

- [53] Pulsinelli WA, Levy DE, Sigsbee B, et al. Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus. *Am J Med* 1983;74:540–4.
- [54] Siemkowicz E, Gjedde A. Post-ischemic coma in rat: effect of different pre-ischemic blood glucose levels on cerebral metabolic recovery after ischemia. *Acta Physiol Scand* 1980;110: 225–32.
- [55] Warner DS, Gionet TX, Todd MM, et al. Insulin-induced normoglycemia improves ischemic outcome in hyperglycemic rats. *Stroke* 1992;23:1775–80.
- [56] Dietrich WD, Busto R, Globus MY, et al. Brain damage and temperature: cellular and molecular mechanisms. *Adv Neurol* 1996;71:177–99.
- [57] Katz L, Ebmeyer U, Safar P, et al. Outcome model of asphyxial cardiac arrest in rats. *J Cereb Blood Flow Metab* 1995;15:1032–9.
- [58] Riepe MW, Kasischke K, Raupach: acetylsalicylic acid increases tolerance against hypoxic and chemical hypoxia. *Stroke* 1997;28(10):2006–11.
- [59] Vaughan DJ, Delanty N. Neuroprotective properties of statins in cerebral ischemia and stroke. *Stroke* 1999;30:1969–73.