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Review article

Impact of anesthetic agents on cerebrovascular physiology in children

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Summary

The role of the pediatric neuroanesthetist is to provide comprehensive care to children with neurologic pathologies. The cerebral physiology is influenced by the developmental stage of the child. The understanding of the effects of anesthetic agents on the physiology of cerebral vasculature in the pediatric population has significantly increased in the past decade allowing a more rationale decision making in anesthesia management. Although no single anesthetic technique can be recommended, sound knowledge of the principles of cerebral physiology and anesthetic neuropharmacology will facilitate the care of pediatric neurosurgical patients.

Keywords: pediatric neuroanesthesia; cerebral blood flow; cerebrovascular regulation; neuropharmacology of anesthetic agents

Introduction

Anesthesia for neurosurgery in children differs from adults because of numerous age-related anatomic and physiologic reasons. Although adolescent neuroanesthesia management inferences can be made from adult neurosurgical and -anesthetic literature, available information for infants and children is scarce. This paper reviews the neurophysiology and -pharmacology considerations pertinent to the management of anesthesia in the pediatric neurosurgical patient with particular attention to cerebrovascular physiology and its modulation by anesthetic agents.

Physiology

Cerebrospinal fluid

The functional integrity of the brain depends on a tightly controlled *milieu intérieur*. The cerebrospinal fluid (CSF) ensures maintenance of this internal environment and shields the brain from homeostatic disturbances, such as acute changes in the serum concentrations of electrolytes (e.g. Na^+, K^+). CSF is produced by active and passive membrane transport mainly in the choroid plexus in the cerebral ventricles. Although it is less in premature babies and small infants, the rate of CSF formation is relatively constant, between 0.3 and 0.4 $ml \cdot min^{-1}$ in both adults and children (1,2). Because the CSF reservoir system is smaller in children, CSF turnover rate is higher, contributing to a faster increase in intracranial pressure (ICP) in the presence of a noncommunicating hydrocephalus (3). The arachnoid villi are responsible for the passive process of CSF absorption. The rate of absorption depends on the CSF-to-venous pressure gradient and the absorption resistance. Villi allow flow of CSF into cerebral sinuses at a pressure difference of 1.5 mmHg or greater (4). Under normal conditions, the production and absorption of CSF is balanced, however, reduction of CSF production by one third reduces ICP by

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only 1.1 mmHg (1). Accordingly, a reduction in CSF production by acetazolamide or furosemide has only minimal effects on ICP unless the patient's intracranial compliance is significantly decreased.

Intracranial pressure

Intracranial pressure is age-dependent, with 0–6, 6–11, and 13–15 mmHg representing normal levels in infants, toddlers, and adolescents, respectively (5). However, ICP can be negative in premature infants and term neonates (5). The open fontanels and floating calvarial bone plates in infants allow for slow increases in intracerebral volume and ICP. The fontanel can also provide a way of monitoring ICP. The dura is a non-elastic membrane that does not allow a rapidly expanding space-occupying processes to be accommodated. Therefore, ventriculoperitoneal shunt malfunction, sub- or epidural hemorrhage or cerebral edema following traumatic brain injury (TBI), will quickly result in increased ICP despite the presence of open fontanels and unfused sutures.

Determinants of cerebral blood flow

Cerebral blood flow (CBF) and metabolism are a function of age (Figure 1). Global CBF is lower in premature infants and term neonates (40–50 ml·100 g^{-1}·min^{-1}) and higher in infants and children aged from 6 months to 3 years (70–110 ml·100 g^{-1}·min^{-1}) than in adults (50 ml·100 g^{-1}·min^{-1}) (6). The pattern of regional cerebral blood flow (rCBF) is also age-dependent. The grey matter of children has a markedly higher rCBF, and there is a lack of frontal predominance when compared with adults. The adult distribution pattern of rCBF is attained by early adolescence (7–10).

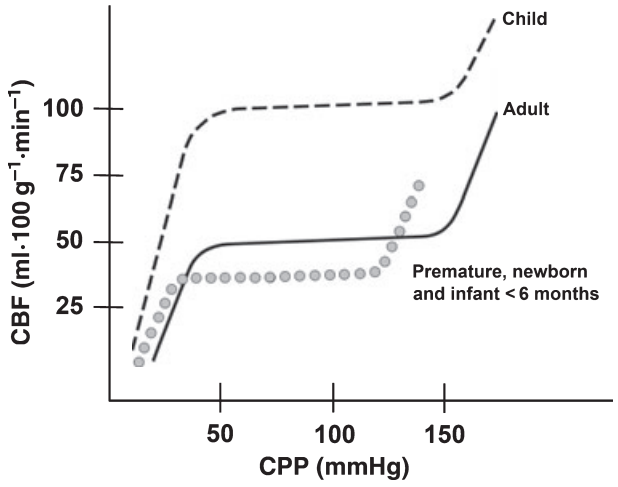

Figure 1
Cerebral blood flow is age dependent. Adapted from reference (6).

Cerebral metabolic rate for oxygen ($CMRO_2$) is one of the determinants of CBF as supply and demand are closely coupled in the brain. In children, $CMRO_2$ is higher (5.5 ml·100 g^{-1}·min^{-1}) than in adults (3.5 ml·100 g^{-1}·min^{-1}), and its distribution parallels the distribution of rCBF described earlier (10). Likewise, the pediatric brain consumes 6.8 mg of glucose per 100 g of tissue per minute, whereas the adult brain consumes 5.5 mg·100 g^{-1}·min^{-1} (11).

Apart from the metabolic demands, CBF is further determined by cerebral perfusion pressure (CPP) and the arterial oxygen (PaO_2) and carbon dioxide tensions ($PaCO_2$). CPP is the difference between mean arterial pressure (MAP) measured at the level of the external ear canal, and the effective downstream pressure across the cerebral vascular bed, which is determined by the highest value of central venous pressure, ICP, or zero flow pressure vascular tone.

The idea of zero flow pressure originates from the application of Laplace's law to vessels with active wall tension (12), and is determined as follows: while continuously decreasing perfusion pressure, there is a point, the zero flow pressure, below which the transmural hydrostatic pressure is not sufficient to counteract wall tension, and the vessel collapses. Correspondingly, if the wall tension is greater, the closing pressure will be higher. This has been consistently confirmed in multiple recent studies, where changing $PaCO_2$ and thereby altering cerebral vascular tone caused reciprocal changes in zero flow pressure (13–15). A direct association between zero flow pressure and MAP has been reported in neonates (16), likely reflecting cerebral autoregulation causing an increase in wall tension in response to an increase in MAP. In contrast, in a maximally dilated vascular bed, such as after severe head trauma, the effective downstream pressure of the cerebral circulation is the ICP (17,18). Propofol and sevoflurane have been shown to exert opposing effects on zero flow pressure (19). This well-described impact on cerebral vasculature will be discussed later.

Cerebral autoregulation

Autoregulation of the cerebral vasculature maintains CBF constant when CPP varies between 50–150 mmHg of MAP in adults (20,21). Outside this range cerebral perfusion becomes systemic blood pressure dependent, increasing the potential for ischemia below the lower limit of autoregulation (LLA) and cerebral edema and/or hemorrhage above the upper limit (22). Studies have confirmed the presence of dynamic and static autoregulation in the normotensive preterm baby (23), full term neonate (24), and young child (25), but the autoregulatory limits remain largely undefined. Munro *et al.* (23) determined CBF in preterm neonates using near-infrared spectroscopy and calculated an LLA of 30 mmHg. Vavilala *et al.* (26) studied static autoregulation using transcranial Doppler ultrasonography in children aged 6 months or older, and identified a LLA of 60 mmHg regardless of age. This value is close to the resting MAP of younger children, predicting a significantly lower autoregulatory reserve in this age group. More recently, using the transient hyperemic response test, Wong *et al.* (27) demonstrated that dynamic autoregulation is preserved in the presence of increasing sevoflurane concentrations in young children. As this transient hyperemic response is present despite estimated MCA pressures well below 60 mmHg, one could speculate that the LLA is lower than this value in children aged 1.5–2.5 years. Cerebral autoregulation is believed to be impaired in critically ill preterm neonates (22,28,29), following moderate to severe TBI in children (30), and in the penumbra surrounding brain tumors (31). In addition, autoregulation is attenuated by vasodilating agents, such as nitroprusside, high concentrations of volatile anesthetics (32), or hypercapnia (33).

Cerebrovascular reactivity to carbon dioxide and oxygen tensions

In adults, there is a linear relationship between CBF and the $PaCO_2$ between 20 and 80 mmHg. This cerebrovascular reactivity to carbon dioxide (CCO_2R) forms the basis of the immediate bedside management of a life-threatening increase in ICP. CBF and therefore, cerebral blood volume, responds rapidly to changes in $PaCO_2$ and reaches a plateau within 2 min. However, hyperventilation is only effective for 4–8 h, after which CBF is gradually reset to its initial value reflecting normalization of pH in the CSF (21,34). In children, CCO_2R is logarithmic with a maximum vasodilatory effect reached at around 50 mmHg (35). Arterial hypotension appears to impair CO_2 reactivity (33).

In adults, CBF is unaffected by decreases in PaO_2 until a partial pressure of 60 mmHg is reached, below which an exponential increase in CBF occurs (21,36,37). In contrast, hyperoxia (PaO_2 > 300 mmHg) causes cerebral vasoconstriction and reduces CBF in the adult (37,38). There is some evidence that cerebral oxygen vasoreactivity is affected by vascular diseases and TBI (39,40). Fetal and neonatal circulation have a heightened response to decreases in PaO_2 possibly reflecting the increased oxygen affinity of fetal hemoglobin (41).

Rheology

Blood viscosity has been suggested as an independent regulator of CBF (42,43), and may help to explain the mechanism by which mannitol decreases ICP. According to the Hagen–Poiseuille law, decreasing viscosity of a fluid increases its flow. The effect of rheology on cerebral autoregulation is called rheology-autoregulation and refers to the ability of cerebral vessels to dilate or constrict in response to increased or decreased viscosity. In the context of ICP management, administration of mannitol as a bolus decreases blood viscosity thereby augmenting CBF, which in the presence of intact autoregulation leads to vasoconstriction and decreased cerebral blood volume (44). Further analysis of the response revealed that the active changes in vessel diameter reflect an oxygen-dependent mechanism that attempts to maintain cerebral oxygen delivery constant (45).

In conclusion, comparatively little is known about the regulation of CBF in the newborn, infant, and young child. While autoregulation is likely present in the healthy newborn, the range of autoregulation has not been determined. In addition, critically ill neonates may present with pressure passive cerebral perfusion. Without exact knowledge of normal CPP and the potential for cerebral edema and/or intraventricular hemorrhage in the preterm infant with supra-normal CPP, it is difficult to make

evidence-based recommendations for the management of these children in the critical care setting.

Pharmacology

Volatile anesthetic agents

Nitrous oxide. Nitrous oxide is a cerebrovasodilator when used alone (46–49) or as an adjunct to volatile agents (50–55) or propofol (56,57) in both adults, and children. More specifically, N_2O increases regional CBF and regional CBV in supratentorial grey matter. This is in contrast to the global cerebral vasodilatation produced by CO_2 (46,47). The exact mechanism behind this cerebral vasodilatation is not known, however, mitochondrial activation (46,53,54,58,59), and sympathoadrenal stimulation (60,61) have been suggested. According to the experimental data, N_2O increases $CMRO_2$ when given alone (62) or in combination (63–65) with other anesthetic drugs. Nitrous oxide does not affect CCO_2R in adults (66–69) and in children during propofol anesthesia (70). The addition of N_2O to 1.5 MAC sevoflurane significantly reduces CCO_2R in the hypocapnic range in children (71). Cerebral autoregulation is impaired when N_2O is used either as a sole hypnotic agent (72) or when it is used in combination with sevoflurane (55,73). In conclusion, as N_2O has the ability to impair autoregulation and CCO_2R, increases CBF and $CMRO_2$, and potentially ICP, it should be avoided in patients at risk for impaired cerebral perfusion.

Halogenated inhalational anesthetics. All potent volatile anesthetics are direct cerebral vasodilators. Halothane is widely regarded as the most potent (74). In children, halothane induced increases in CBF persist even after halothane concentrations have been decreased (75). This cerebrovascular hysteresis phenomenon is not present during isoflurane anesthesia (76). Matta *et al.* (77) found that at propofol-induced maximal EEG suppression halothane produces less cerebral vasodilatation than isoflurane or desflurane. Among all inhalational agents, sevoflurane has the least effect at equipotent concentrations (77). In children, Leon *et al.* (78) demonstrated no significant difference in CBF velocity between isoflurane and halothane at 0.5 and 1.0 MAC at the same end tidal CO_2 values. The 'dual action hypothesis' (79,80) attempts to provide an explanation for these conflicting results of inhalation anesthetics on the cerebral vasculature. This hypothesis states that apart from the direct cerebral vasodilatory action, CBF will also be determined by functional flow-metabolism coupling and the anesthetic-induced decrease in $CMRO_2$. Both, isoflurane and sevoflurane reduce the $CMRO_2$ to a greater extent than halothane.(81) Of the newer halogenated agents, desflurane seems to be the most potent cerebral vasodilator, whereas sevoflurane causes the least increase in CBF and CBV in both adults (77,82,83) and children (50,84–86).

Children, in general, seem to have an increased sensitivity to the cerebral vasodilatory effects of inhalational anesthetic agents (78). For instance, cerebral vasodilatation is already maximal at 1.0 MAC of desflurane in normocapnic children (84), whereas in adults (77) 1.5 MAC resulted in a further increase in CBF. Although isoflurane causes significant impairment of cerebral autoregulation at clinical concentrations (32), hypocapnia restores cerebral autoregulation during isoflurane anesthesia at 1.4 MAC (87).

In adults, cerebral autoregulation is preserved up to 1.5 MAC of sevoflurane (55,88,89). Higher doses of sevoflurane (2.0 MAC) (90) or the combination of hypercapnia (endtidal CO_2 of 50 mm Hg) (91) and lower sevoflurane concentrations decrease the autoregulatory capacity. Dynamic cerebral autoregulation, i.e. the fast component of autoregulation in response to acute changes in pressure pulsations, as opposed to the slow static reaction in response to changes in MAP, is marginally impaired at 1.5 MAC sevoflurane in adults (88). In young children, similar to older children and adults, CBF is unaffected up to 1.5 MAC of sevoflurane (86), and autoregulation is maintained with low concentrations (<1.0 MAC) of sevoflurane (25). In addition, dynamic autoregulation in young children remains functional up to 1.5 MAC of sevoflurane (27). The effects of desflurane on cerebral autoregulation in the pediatric population has not been evaluated, one may speculate that its powerful vasodilatory effect must affect it. In adults, cerebral autoregulation is impaired at 1.0 MAC, and nearly abolished at 1.5 MAC of desflurane (92).

In general, cerebrovascular carbon dioxide reactivity is maintained during the administration of inhalational anesthesia. In contrast to adults, there is a loss of response beyond 45–50 mmHg of endtidal CO_2 (78,93,94), because maximal cerebral vasodilatation is reached in this age group (Figure 2) (35). Changes in $PaCO_2$ result in more pronounced changes in CBF in the presence of sevoflurane (93) than with other volatile anesthetics, further emphasizing the comparably moderate actions of this agent on the cerebral vasculature.

Discussion of the neuroprotective and preconditioning properties of inhalational anesthetics is beyond the scope of the present paper. The interested reader is referred to recently published reviews of the subject (95–97).

In summary, the cerebral vasculature of children seems to have a heightened response to inhalational anesthetics with maximal cerebral vasodilatation achieved at lower concentrations when compared with adults. While desflurane has the lowest blood-gas partition coefficient allowing for fast emergence from general anesthesia, its effects on the cerebral vasculature are the least favorable among the newer inhalational agents (98). Sevoflurane and isoflurane appear to be superior volatile anesthetics for neuroanesthesia.

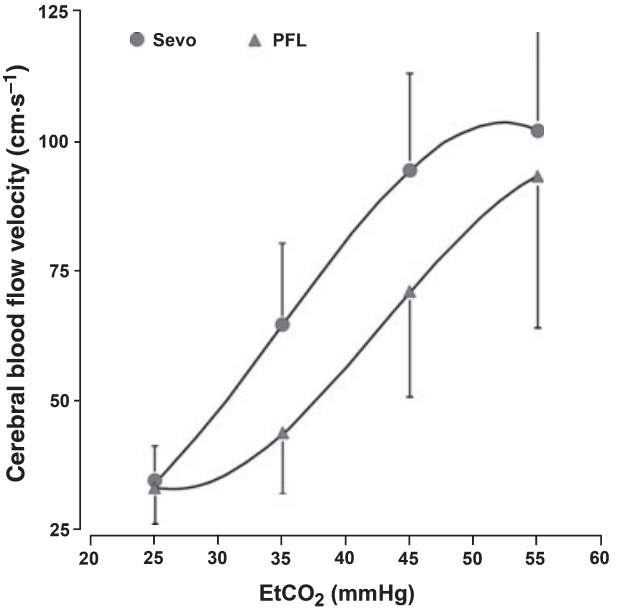

Figure 2
Cerebrovascular reactivity to CO_2 in children assessed by transcranial Doppler ultrasound of the middle cerebral artery in the presence of propofol and sevoflurane. Adapted from reference (113), see text for details.

Intravenous anesthetic agents

Thiopental. Sodium thiopental is considered an exemplary neuroprotective agent in clinical practice. It decreases CBF, CBV, and $CMRO_2$ in a dose-dependent manner and consequently reduces ICP, while at the same time maintaining autoregulation and CCO_2R. Thiopental may reduce myocardial contractility, arterial blood pressure, and CPP. The neuroprotective effect of thiopental *in vivo* is believed to be a result of decreased $CMRO_2$. Sodium thiopental attenuates ischemia-induced glutamate release (99), and inhibits cortical intracellular calcium increase (100). Its sulphydryl moiety seems to provide additional brain protection via free radical scavenging *in vitro* (101). Sodium thiopental is capable of reducing the extent of cerebral damage in focal cerebral ischemia (102,103), and in cerebral edema induced by cortical freeze injury in animal studies (104).

Propofol. Propofol appears to have the properties of an ideal hypnotic agent for neurosurgical procedures. It is a cerebral vasoconstrictor that reduces CBF and $CMRO_2$ in a dose dependent manner in both children (105) and adults (106). Its rapid redistribution from the central compartment and fast metabolic clearance allows for an early and predictable emergence making it suitable for maintenance of anesthesia by continuous infusion. Propofol may have neuroprotective effects during ischemia (107–109), but seems, at least *in vitro*, inferior in this regard to thiopental (110), Propofol preserves cerebral autoregulation and CCO_2R (111,112). In contrast to adults, CCO_2R seems maximal below a $PaCO_2$ level of 30 mmHg in children anesthetized with propofol (113). It is conceivable that the combined cerebral vasoconstrictive effect of propofol anesthesia and an endtidal CO_2 below 30 mmHg is near maximal, increasing the risk of iatrogenically induced cerebral ischemia (Figure 2). It may be possible that the propofol-induced increase in cerebral vascular tone will lead to an increase in zero flow pressure, and ultimately decrease effective CPP (19). The clinical significance of increased zero flow pressure has not been

investigated, but caution should be exercised in the presence of concurrent hypotension.

Etomidate. Etomidate reduces ICP by decreasing CBF and $CMRO_2$, and produces less cardiovascular depression than propofol or thiopental (114). Etomidate was generally assumed to have neuroprotective effects (115) by its virtue of decreasing $CMRO_2$ (116), and was used during temporary arterial occlusion in cerebrovascular procedures to this effect (117,118). More recently, the neuroprotective effect has been called into question, particularly in the context of focal ischemia (119,120). Etomidate decreases CBF by increasing cerebral vascular resistance at levels far below those that would cause a decrease in $CMRO_2$ (121), and significant reduction of brain tissue oxygenation to ischemic levels develops (122,123). The increased vascular resistance seems to be related to inhibition of nitric oxide synthase by etomidate (124). Etomidate is well known to cause suppression of the adrenocortical system (125), further cautioning against its use in neurocritical care.

Ketamine. Ketamine is an N-methyl-D-aspartate antagonist with proven neuroprotective effects both, *in vivo* (126,127), and *in vitro* (128–130). However, it is also a potent cerebral vasodilator producing increases in CBF, CBV, $CMRO_2$ and potentially ICP, and can not be recommended in patients with reduced intracranial compliance (74,131–133).

Benzodiazepines. In healthy adults, benzodiazepines reduce global CBF and $CMRO_2$ (134–136), and maintain cerebrovascular reactivity to carbon dioxide (53,137). At sedative doses the decrease in CBF is approximately 10% (134,138), while at anesthetic levels it is approximately 30% (136) with an apparent ceiling effect (139). Further studies reveal specific decreases in regional CBF (134,135,138) and glucose metabolism (140) caused by benzodiazepines in areas of the brain involved in memory formation and arousal.

The benzodiazepine antagonist flumazenil when administered alone is devoid of any effect on cerebral physiology (141,142). When given after midazolam or lorazepam, it reverses their cerebrovascular and metabolic effects (138,142) with the probability of an increase in ICP (143). In contrast, Knudsen *et al.* demonstrated that flumazenil had no effect on CBF and $CMRO_2$ when used for reversal of midazolam anesthesia for craniotomy (144).

Studies on the cerebrovascular effects of benzodiazepines in the pediatric population are scarce, and mainly relate to their safe use in premature infants (145–147) with similar sedation-related decreases in CBF (145,147) as seen in adults.

Opioids. In general, opioids have little or no effect on CBF, $CMRO_2$, and ICP. Cerebrovascular reactivity to carbon dioxide and autoregulation appear preserved. Opioids may indirectly decrease CBF by blocking catecholamine release in patients experiencing pain (33). In this regard, it is particularly advantageous to blunt the hemodynamic response to direct laryngoscopy in patients with increased ICP or cerebrovascular pathology.

In children, a study (148) comparing equipotent remifentanil and fentanyl infusions during induction and direct laryngoscopy reported better hemodynamic stability with fentanyl. Specifically, remifentanil, but not fentanyl, caused a significant decrease in MAP and CBF prior to tracheal intubation, and could not prevent a sudden increase in CBF during laryngoscopy (148). However, remifentanil, which has a very short half-life and constant context-sensitive half time (149,150), does not impair CCO_2R even at high doses (151), seems to be an ideal analgesic agent during the maintenance of anesthesia for neurosurgery.

Conclusion

The role of the pediatric neuroanesthetist is to provide comprehensive care to children with neurologic pathologies. The cerebral physiology is influenced by the developmental stage of the child. The understanding of the effects of anesthetic agents on the physiology of cerebral vasculature in the pediatric population has significantly increased in the past decade allowing a more rationale decision making in anesthesia management. Although no single anesthetic technique can be recommended, sound knowledge of the principles of cerebral physiology and anesthetic neuropharmacology will facilitate the care of pediatric neurosurgical patients.

References

1 Cutler RW, Page L, Galicich J *et al.* Formation and absorption of cerebrospinal fluid in man. *Brain* 1968; **91:** 707–720.
2 Watters GV, Cutler RW. Cerebrospinal fluid formation and reabsorption in children. *Neurology* 1968; **18:** 296.
3 Marmarou A, Shulman K, LaMorgese J. Compartmental analysis of compliance and outflow resistance of the cerebrospinal fluid system. *J Neurosurg* 1975; **43:** 523–534.
4 Daveson H. *Physiology of cerebrospinal fluid*. Boston: Little Brown, 1967.
5 Welch K. The intracranial pressure in infants. *J Neurosurg* 1980; **52:** 693–699.
6 Davis A, Ravussin P, Bissonnette B. Central Nervous System: Anatomy and Physiology. In: Bissonnette BD, Dalens B, eds. *Pediatric Anesthesia, Principles and Practice*, 1st edn. New York: McGraw-Hill, 2002: pp. 104–113.
7 Borch K, Greisen G. Blood flow distribution in the normal human preterm brain. *Pediatr Res* 1998; **43:** 28–33.
8 Chiron C, Raynaud C, Maziere B *et al.* Changes in regional cerebral blood flow during brain maturation in children and adolescents. *J Nucl Med* 1992; **33:** 696–703.
9 Ogawa A, Sakurai Y, Kayama T *et al.* Regional cerebral blood flow with age: changes in rCBF in childhood. *Neurol Res* 1989; **11:** 173–176.
10 Takahashi T, Shirane R, Sato S *et al.* Developmental changes of cerebral blood flow and oxygen metabolism in children. *AJNR Am J Neuroradiol* 1999; **20:** 917–922.
11 Wass CT, Lanier WL. Glucose modulation of ischemic brain injury: review and clinical recommendations. *Mayo Clin Proc* 1996; **71:** 801–812.
12 Panerai RB. The critical closing pressure of the cerebral circulation. *Med Eng Phys* 2003; **25:** 621–632.
13 Hancock SM, Mahajan RP, Athanassiou L. Noninvasive estimation of cerebral perfusion pressure and zero flow pressure in healthy volunteers: the effects of changes in end-tidal carbon dioxide. *Anesth Analg* 2003; **96:** 847–851, table of contents.
14 Panerai RB, Deverson ST, Mahony P *et al.* Effects of CO2 on dynamic cerebral autoregulation measurement. *Physiol Meas* 1999; **20:** 265–275.
15 Weyland A, Buhre W, Grund S *et al.* Cerebrovascular tone rather than intracranial pressure determines the effective downstream pressure of the cerebral circulation in the absence of intracranial hypertension. *J Neurosurg Anesthesiol* 2000; **12:** 210–216.
16 Panerai RB, Kelsall AW, Rennie JM *et al.* Estimation of critical closing pressure in the cerebral circulation of newborns. *Neuropediatrics* 1995; **26:** 168–173.
17 Buhre W, Heinzel FR, Grund S *et al.* Extrapolation to zero-flow pressure in cerebral arteries to estimate intracranial pressure. *Br J Anaesth* 2003; **90:** 291–295.
18 Czosnyka M, Smielewski P, Piechnik S *et al.* Critical closing pressure in cerebrovascular circulation. *J Neurol Neurosurg Psychiatry* 1999; **66:** 606–611.
19 Marval PD, Perrin ME, Hancock SM *et al.* The effects of propofol or sevoflurane on the estimated cerebral perfusion pressure and zero flow pressure. *Anesth Analg* 2005; **100:** 835–840, table of contents.
20 Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990; **2:** 161–192.
21 Lassen NA, Christensen MS. Physiology of cerebral blood flow. *Br J Anaesth* 1976; **48:** 719–734.
22 Milligan DW. Failure of autoregulation and intraventricular haemorrhage in preterm infants. *Lancet* 1980; **1:** 896–898.
23 Munro MJ, Walker AM, Barfield CP. Hypotensive extremely low birth weight infants have reduced cerebral blood flow. *Pediatrics* 2004; **114:** 1591–1596.
24 Hillier SC, Burrows FA, Bissonnette B *et al.* Cerebral hemodynamics in neonates and infants undergoing cardiopulmonary bypass and profound hypothermic circulatory arrest: assessment by transcranial Doppler sonography. *Anesth Analg* 1991; **72:** 723–728.
25 Vavilala MS, Lee LA, Lee M *et al.* Cerebral autoregulation in children during sevoflurane anaesthesia. *Br J Anaesth* 2003; **90:** 636–641.
26 Vavilala MS, Lee LA, Lam AM. The lower limit of cerebral autoregulation in children during sevoflurane anesthesia. *J Neurosurg Anesthesiol* 2003; **15:** 307–312.
27 Wong GT, Luginbuehl I, Karsli C *et al.* The effect of sevoflurane on cerebral autoregulation in young children as assessed by the transient hyperemic response. *Anesth Analg* 2006; **102:** 1051–1055.
28 Lou HC, Lassen NA, Friis-Hansen B. Impaired autoregulation of cerebral blood flow in the distressed newborn infant. *J Pediatr* 1979; **94:** 118–121.
29 Rosenbaum JL, Almli CR, Yundt KD *et al.* Higher neonatal cerebral blood flow correlates with worse childhood neurologic outcome. *Neurology* 1997; **49:** 1035–1041.
30 Vavilala MS, Lee LA, Boddu K *et al.* Cerebral autoregulation in pediatric traumatic brain injury. *Pediatr Crit Care Med* 2004; **5:** 257–263.
31 Schmieder K, Schregel W, Harders A *et al.* Dynamic cerebral autoregulation in patients undergoing surgery for intracranial tumors. *Eur J Ultrasound* 2000; **12:** 1–7.
32 Strebel S, Lam AM, Matta B *et al.* Dynamic and static cerebral autoregulation during isoflurane, desflurane, and propofol anesthesia. *Anesthesiology* 1995; **83:** 66–76.
33 Bracco D, Bissonnette B. Neurosurgery and Neurotraumatology: Anesthetic Consideration and Postoperative Management. In: Bissonnette BD, Dalens B, eds. *Pediatric Anesthesia, Principles and Practice*, 1st edn. New York: McGraw-Hill, 2002.
34 Severinghaus JW, Lassen N. Step hypocapnia to separate arterial from tissue PCO2 in the regulation of cerebral blood flow. *Circ Res* 1967; **20:** 272–278.
35 Pilato MA, Bissonnette B, Lerman J. Transcranial Doppler: response of cerebral blood-flow velocity to carbon dioxide in anaesthetized children. *Can J Anaesth* 1991; **38:** 37–42.
36 Gupta AK, Menon DK, Czosnyka M *et al.* Thresholds for hypoxic cerebral vasodilation in volunteers. *Anesth Analg* 1997; **85:** 817–820.
37 Johnston AJ, Steiner LA, Gupta AK *et al.* Cerebral oxygen vasoreactivity and cerebral tissue oxygen reactivity. *Br J Anaesth* 2003; **90:** 774–786.
38 Watson NA, Beards SC, Altaf N *et al.* The effect of hyperoxia on cerebral blood flow: a study in healthy volunteers using magnetic resonance phase-contrast angiography. *Eur J Anaesthesiol* 2000; **17:** 152–159.
39 Amano T, Meyer JS, Okabe T *et al.* Cerebral vasomotor responses during oxygen inhalation. *Results in normal aging and dementia. Arch Neurol* 1983; **40:** 277–282.
40 Menzel M, Doppenberg EM, Zauner A *et al.* Cerebral oxygenation in patients after severe head injury: monitoring and effects of arterial hyperoxia on cerebral blood flow,

metabolism and intracranial pressure. *J Neurosurg Anesthesiol* 1999; **11:** 240–251.
41 Rogers MC, Nugent SK, Traystman RJ. Control of cerebral circulation in the neonate and infant. *Crit Care Med* 1980; **8:** 570–574.
42 Hudak ML, Jones MD Jr, Popel AS *et al.* Hemodilution causes size-dependent constriction of pial arterioles in the cat. *Am J Physiol* 1989; **257:** H912–917.
43 Muizelaar JP, Wei EP, Kontos HA *et al.* Mannitol causes compensatory cerebral vasoconstriction and vasodilation in response to blood viscosity changes. *J Neurosurg* 1983; **59:** 822–828.
44 Muizelaar JP, Lutz HA 3rd, Becker DP. Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head-injured patients. *J Neurosurg* 1984; **61:** 700–706.
45 Rebel A, Ulatowski JA, Kwansa H *et al.* Cerebrovascular response to decreased hematocrit: effect of cell-free hemoglobin, plasma viscosity, and CO2. *Am J Physiol Heart Circ Physiol* 2003; **285:** H1600–1608.
46 Leon JE, Bissonnette B. Transcranial Doppler sonography: nitrous oxide and cerebral blood flow velocity in children. *Can J Anaesth* 1991; **38:** 974–979.
47 Lorenz IH, Kolbitsch C, Hormann C *et al.* Influence of equianaesthetic concentrations of nitrous oxide and isoflurane on regional cerebral blood flow, regional cerebral blood volume, and regional mean transit time in human volunteers. *Br J Anaesth* 2001; **87:** 691–698.
48 Reinstrup P, Ryding E, Algotsson L *et al.* Effects of nitrous oxide on human regional cerebral blood flow and isolated pial arteries. *Anesthesiology* 1994; **81:** 396–402.
49 Field LM, Dorrance DE, Krzeminska EK *et al.* Effect of nitrous oxide on cerebral blood flow in normal humans. *Br J Anaesth* 1993; **70:** 154–159.
50 Karsli C, Luginbuehl IA, Bissonnette B. The effect of nitrous oxide on cerebral blood flow velocity in children anaesthetised with desflurane. *Anaesthesia* 2003; **58:** 24–27.
51 Rowney DA, Fairgrieve R, Bissonnette B. The effect of nitrous oxide on cerebral blood flow velocity in children anaesthetised with sevoflurane. *Anaesthesia* 2004; **59:** 10–14.
52 Cho S, Fujigaki T, Uchiyama Y *et al.* Effects of sevoflurane with and without nitrous oxide on human cerebral circulation. *Transcranial Doppler study. Anesthesiology* 1996; **85:** 755–760.
53 Strebel S, Kaufmann M, Anselmi L *et al.* Nitrous oxide is a potent cerebrovasodilator in humans when added to isoflurane. *A transcranial Doppler study. Acta Anaesthesiol Scand* 1995; **39:** 653–658.
54 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:** 462–468.
55 Bedforth NM, Girling KJ, Harrison JM *et al.* The effects of sevoflurane and nitrous oxide on middle cerebral artery blood flow velocity and transient hyperemic response. *Anesth Analg* 1999; **89:** 170–174.
56 Harrison JM, Girling KJ, Mahajan RP. Effects of propofol and nitrous oxide on middle cerebral artery flow velocity and cerebral autoregulation. *Anaesthesia* 2002; **57:** 27–32.
57 Wilson-Smith E, Karsli C, Luginbuehl IA *et al.* The effect of nitrous oxide on cerebral blood flow velocity in children anesthetized with propofol. *Acta Anaesthesiol Scand* 2003; **47:** 307–311.
58 Matta BF, Lam AM. Nitrous oxide increases cerebral blood flow velocity during pharmacologically induced EEG silence in humans. *J Neurosurg Anesthesiol* 1995; **7:** 89–93.
59 Becker GL, Pelligrino DA, Miletich DJ *et al.* The effects of nitrous oxide on oxygen consumption by isolated cerebral cortex mitochondria. *Anesth Analg* 1986; **65:** 355–359.
60 Nakanishi O, Ishikawa T, Imamura Y *et al.* Inhibition of cerebral metabolic and circulatory responses to nitrous oxide by 6-hydroxydopamine in dogs. *Can J Anaesth* 1997; **44:** 1008–1013.
61 Fukuhara N, Ishikawa T, Kinoshita H *et al.* Central noradrenergic mediation of nitrous oxide-induced analgesia in rats. *Can J Anaesth* 1998; **45:** 1123–1129.
62 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:** 405–412.
63 Algotsson L, Messeter K, Rosen I *et al.* Effects of nitrous oxide on cerebral haemodynamics and metabolism during isoflurane anaesthesia in man. *Acta Anaesthesiol Scand* 1992; **36:** 46–52.
64 Roald OK, Forsman M, Heier MS *et al.* Cerebral effects of nitrous oxide when added to low and high concentrations of isoflurane in the dog. *Anesth Analg* 1991; **72:** 75–79.
65 Kaisti KK, Langsjo JW, Aalto S *et al.* Effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption, and blood volume in humans. *Anesthesiology* 2003; **99:** 603–613.
66 Hormann C, Schmidauer C, Haring HP *et al.* Hyperventilation reverses the nitrous oxide-induced increase in cerebral blood flow velocity in human volunteers. *Br J Anaesth* 1995; **74:** 616–618.
67 Aono M, Sato J, Nishino T. Nitrous oxide increases normocapnic cerebral blood flow velocity but does not affect the dynamic cerebrovascular response to step changes in end-tidal P(CO2) in humans. *Anesth Analg* 1999; **89:** 684–689.
68 Inaba S, Sato J, Aono M *et al.* Combined effects of nitrous oxide and propofol on the dynamic cerebrovascular response to step changes in end-tidal PCO2 in humans. *Anesthesiology* 2003; **98:** 633–638.
69 Reinstrup P, Ryding E, Ohlsson T *et al.* Cerebral blood volume (CBV) in humans during normo- and hypocapnia: influence of nitrous oxide (N(2)O). *Anesthesiology* 2001; **95:** 1079–1082.
70 Karsli C, Wilson-Smith E, Luginbuehl I *et al.* The effect of nitrous oxide on cerebrovascular reactivity to carbon dioxide in children during propofol anesthesia. *Anesth Analg* 2003; **97:** 694–698.
71 Wilson-Smith E, Karsli C, Luginbuehl I *et al.* Effect of nitrous oxide on cerebrovascular reactivity to carbon dioxide in children during sevoflurane anaesthesia. *Br J Anaesth* 2003; **91:** 190–195.
72 Girling KJ, Cavill G, Mahajan RP. The effects of nitrous oxide and oxygen on transient hyperemic response in human volunteers. *Anesth Analg* 1999; **89:** 175–180.
73 Iacopino DG, Conti A, Battaglia C *et al.* Transcranial Doppler ultrasound study of the effects of nitrous oxide on cerebral autoregulation during neurosurgical anesthesia: a randomized controlled trial. *J Neurosurg* 2003; **99:** 58–64.
74 Sakabe T, Nakakimura K. Effects of anesthetic agents and other drugs on cerebral blood flow, metabolism and intracranial pressure. In: Cottrell JE, Smith DS, eds. *Anesthesia in Neurosurgery*, 4th edn. St Louis: Mosby, 2001: pp. 129–144.

75 Paut O, Bissonnette B. Effect of halothane on the cerebral circulation in young children: a hysteresis phenomenon. *Anaesthesia* 2001; **56:** 360–365.

76 Bisonnette B, Leon JE. Cerebrovascular stability during isoflurane anaesthesia in children. *Can J Anaesth* 1992; **39:** 128–134.

77 Matta BF, Mayberg TS, Lam AM. Direct cerebrovasodilatory effects of halothane, isoflurane, and desflurane during propofol-induced isoelectric electroencephalogram in humans. *Anesthesiology* 1995; **83:** 980–985; discussion 927A.

78 Leon JE, Bissonnette B. Cerebrovascular responses to carbon dioxide in children anaesthetized with halothane and isoflurane. *Can J Anaesth* 1991; **38:** 817–825.

79 Drummond JC, Todd MM, Scheller MS *et al.* A comparison of the direct cerebral vasodilating potencies of halothane and isoflurane in the New Zealand white rabbit. *Anesthesiology* 1986; **65:** 462–467.

80 Hansen TD, Warner DS, Todd MM *et al.* The role of cerebral metabolism in determining the local cerebral blood flow effects of volatile anesthetics: evidence for persistent flow-metabolism coupling. *J Cereb Blood Flow Metab* 1989; **9:** 323–328.

81 Oshima T, Karasawa F, Okazaki Y *et al.* Effects of sevoflurane on cerebral blood flow and cerebral metabolic rate of oxygen in human beings: a comparison with isoflurane. *Eur J Anaesthesiol* 2003; **20:** 543–547.

82 Matta BF, Heath KJ, Tipping K *et al.* Direct cerebral vasodilatory effects of sevoflurane and isoflurane. *Anesthesiology* 1999; **91:** 677–680.

83 Bedforth NM, Hardman JG, Nathanson MH. Cerebral hemodynamic response to the introduction of desflurane: A comparison with sevoflurane. *Anesth Analg*, 2000; **91:** 152–155.

84 Luginbuehl IA, Fredrickson MJ, Karsli C *et al.* Cerebral blood flow velocity in children anaesthetized with desflurane. *Paediatr Anaesth* 2003; **13:** 496–500.

85 Sponheim S, Skraastad O, Helseth E *et al.* Effects of 0.5 and 1.0 MAC isoflurane, sevoflurane and desflurane on intracranial and cerebral perfusion pressures in children. *Acta Anaesthesiol Scand* 2003; **47:** 932–938.

86 Fairgrieve R, Rowney DA, Karsli C *et al.* The effect of sevoflurane on cerebral blood flow velocity in children. *Acta Anaesthesiol Scand* 2003; **47:** 1226–1230.

87 McCulloch TJ, Boesel TW, Lam AM. The effect of hypocapnia on the autoregulation of cerebral blood flow during administration of isoflurane. *Anesth Analg* 2005; **100:** 1463–1467, table of contents.

88 Summors AC, Gupta AK, Matta BF. Dynamic cerebral autoregulation during sevoflurane anesthesia: a comparison with isoflurane. *Anesth Analg* 1999; **88:** 341–345.

89 Gupta S, Heath K, Matta BF. Effect of incremental doses of sevoflurane on cerebral pressure autoregulation in humans. *Br J Anaesth* 1997; **79:** 469–472.

90 Conti A, Iacopino DG, Fodale V *et al.* Cerebral haemodynamic changes during propofol-remifentanil or sevoflurane anaesthesia: transcranial Doppler study under bispectral index monitoring. *Br J Anaesth* 2006; **97:** 333–339.

91 McCulloch TJ, Visco E, Lam AM. Graded hypercapnia and cerebral autoregulation during sevoflurane or propofol anesthesia. *Anesthesiology* 2000; **93:** 1205–1209.

92 Bedforth NM, Girling KJ, Skinner HJ *et al.* Effects of desflurane on cerebral autoregulation. *Br J Anaesth* 2001; **87:** 193–197.

93 Rowney DA, Fairgrieve R, Bissonnette B. Cerebrovascular carbon dioxide reactivity in children anaesthetized with sevoflurane. *Br J Anaesth* 2002; **88:** 357–361.

94 Luginbuehl IA, Karsli C, Bissonnette B. Cerebrovascular reactivity to carbon dioxide is preserved during hypocapnia in children anesthetized with 1.0 MAC, but not with 1.5 MAC desflurane. *Can J Anaesth* 2003; **50:** 166–171.

95 Clarkson AN. Anesthetic-mediated protection/preconditioning during cerebral ischemia. *Life Sci* 2007; **80:** 1157–1175.

96 Head BP, Patel P. Anesthetics and brain protection. *Curr Opin Anaesthesiol* 2007; **20:** 395–399.

97 Kitano H, Kirsch JR, Hurn PD *et al.* Inhalational anesthetics as neuroprotectants or chemical preconditioning agents in ischemic brain. *J Cereb Blood Flow Metab* 2007; **27:** 1108–1128.

98 Barlow R, Karsli C, Luginbuehl I *et al.* Desflurane increases cerebral blood flow velocity when used for rapid emergence from propofol anesthesia in children. *Can J Anaesth* 2004; **51:** 824–828.

99 Amakawa K, Adachi N, Liu K *et al.* Effects of pre- and post-ischemic administration of thiopental on transmitter amino acid release and histologic outcome in gerbils. *Anesthesiology* 1996; **85:** 1422–1430.

100 Zhan RZ, Fujiwara N, Endoh H *et al.* Thiopental inhibits increases in [Ca2+]I induced by membrane depolarization, NMDA receptor activation, and ischemia in rat hippocampal and cortical slices. *Anesthesiology* 1998; **89:** 456–466.

101 Shibuta S, Kosaka J, Mashimo T *et al.* Nitric oxide-induced cytotoxicity attenuation by thiopentone sodium but not pentobarbitone sodium in primary brain cultures. *Br J Pharmacol* 1998; **124:** 804–810.

102 Nussmeier NA, Arlund C, Slogoff S. Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. *Anesthesiology* 1986; **64:** 165–170.

103 Nehls DG, Todd MM, Spetzler RF *et al.* A comparison of the cerebral protective effects of isoflurane and barbiturates during temporary focal ischemia in primates. *Anesthesiology* 1987; **66:** 453–464.

104 Smith AL, Marque JJ. Anesthetics and cerebral edema. *Anesthesiology* 1976; **45:** 64–72.

105 Karsli C, Luginbuehl I, Farrar M *et al.* Propofol decreases cerebral blood flow velocity in anesthetized children. *Can J Anaesth* 2002; **49:** 830–834.

106 Vandesteene A, Trempont V, Engelman E *et al.* Effect of propofol on cerebral blood flow and metabolism in man. *Anaesthesia* 1988; **43**(Suppl)**:** 42–43.

107 Engelhard K, Werner C, Eberspacher E *et al.* Influence of propofol on neuronal damage and apoptotic factors after incomplete cerebral ischemia and reperfusion in rats: a long-term observation. *Anesthesiology* 2004; **101:** 912–917.

108 Bayona NA, Gelb AW, Jiang Z *et al.* Propofol neuroprotection in cerebral ischemia and its effects on low-molecular-weight antioxidants and skilled motor tasks. *Anesthesiology* 2004; **100:** 1151–1159.

109 Ergun R, Akdemir G, Sen S *et al.* Neuroprotective effects of propofol following global cerebral ischemia in rats. *Neurosurg Rev* 2002; **25:** 95–98.

110 Sasaki R, Hirota K, Roth SH *et al.* Anoxic depolarization of rat hippocampal slices is prevented by thiopental but not by propofol or isoflurane. *Br J Anaesth* 2005; **94:** 486–491.

111 Matta BF, Lam AM, Strebel S *et al.* Cerebral pressure autoregulation and carbon dioxide reactivity during propofol-induced EEG suppression. *Br J Anaesth* 1995; **74:** 159–163.

112 Karsli C, Luginbuehl I, Farrar M *et al.* Cerebrovascular carbon dioxide reactivity in children anaesthetized with propofol. *Paediatr Anaesth* 2003; **13:** 26–31.

113 Karsli C, Luginbuehl I, Bissonnette B. The cerebrovascular response to hypocapnia in children receiving propofol. *Anesth Analg* 2004; **99:** 1049–1052, table of contents.
114 Moss E, Powell D, Gibson RM *et al.* Effect of etomidate on intracranial pressure and cerebral perfusion pressure. *Br J Anaesth* 1979; **51:** 347–352.
115 Batjer HH. Cerebral protective effects of etomidate: experimental and clinical aspects. *Cerebrovasc Brain Metab Rev* 1993; **5:** 17–32.
116 Renou AM, Vernhiet J, Macrez P *et al.* Cerebral blood flow and metabolism during etomidate anaesthesia in man. *Br J Anaesth* 1978; **50:** 1047–1051.
117 Batjer HH, Frankfurt AI, Purdy PD *et al.* Use of etomidate, temporary arterial occlusion, and intraoperative angiography in surgical treatment of large and giant cerebral aneurysms. *J Neurosurg* 1988; **68:** 234–240.
118 Rosenwasser RH, Jimenez DF, Wending WW *et al.* Routine use of etomidate and temporary vessel occlusion during aneurysm surgery. *Neurol Res* 1991; **13:** 224–228.
119 Robertson SC, Brown P 3rd, Loftus CM. Effects of etomidate administration on cerebral collateral flow. *Neurosurgery* 1998; **43:** 317–323.
120 Drummond JC, Cole DJ, Patel PM *et al.* Focal cerebral ischemia during anesthesia with etomidate, isoflurane, or thiopental: a comparison of the extent of cerebral injury. *Neurosurgery* 1995; **37:** 742–748.
121 Milde LN, Milde JH, Michenfelder JD. Cerebral functional, metabolic, and hemodynamic effects of etomidate in dogs. *Anesthesiology* 1985; **63:** 371–377.
122 Hoffman WE, Charbel FT, Edelman G *et al.* Comparison of the effect of etomidate and desflurane on brain tissue gases and pH during prolonged middle cerebral artery occlusion. *Anesthesiology* 1998; **88:** 1188–1194.
123 Edelman GJ, Hoffman WE, Charbel FT. Cerebral hypoxia after etomidate administration and temporary cerebral artery occlusion. *Anesth Analg* 1997; **85:** 821–825.
124 Drummond JC, McKay LD, Cole DJ, *et al.* The role of nitric oxide synthase inhibition in the adverse effects of etomidate in the setting of focal cerebral ischemia in rats. *Anesth Analg* 2005; **100:** 841–846, table of contents.
125 Wagner RL, White PF, Kan PB *et al.* Inhibition of adrenal steroidogenesis by the anesthetic etomidate. *N Engl J Med* 1984; **310:** 1415–1421.
126 Church J, Zeman S, Lodge D. The neuroprotective action of ketamine and MK-801 after transient cerebral ischemia in rats. *Anesthesiology* 1988; **69:** 702–709.
127 Hoffman WE, Pelligrino D, Werner C *et al.* Ketamine decreases plasma catecholamines and improves outcome from incomplete cerebral ischemia in rats. *Anesthesiology* 1992; **76:** 755–762.
128 Himmelseher S, Pfenninger E, Georgieff M. The effects of ketamine-isomers on neuronal injury and regeneration in rat hippocampal neurons. *Anesth Analg* 1996; **83:** 505–512.
129 Basagan-Mogol E, Buyukuysal RL, Korfali G. Effects of ketamine and thiopental on ischemia reoxygenation-induced LDH leakage and amino acid release from rat striatal slices. *J Neurosurg Anesthesiol* 2005; **17:** 20–26.
130 Shibuta S, Varathan S, Mashimo T. Ketamine and thiopental sodium: individual and combined neuroprotective effects on cortical cultures exposed to NMDA or nitric oxide. *Br J Anaesth* 2006; **97:** 517–524.
131 Langsjo JW, Kaisti KK, Aalto S *et al.* Effects of subanesthetic doses of ketamine on regional cerebral blood flow, oxygen consumption, and blood volume in humans. *Anesthesiology* 2003; **99:** 614–623.
132 Langsjo JW, Maksimow A, Salmi E *et al.* S-ketamine anesthesia increases cerebral blood flow in excess of the metabolic needs in humans. *Anesthesiology* 2005; **103:** 258–268.
133 Nagels W, Demeyere R, Van Hemelrijck J *et al.* Evaluation of the neuroprotective effects of S(+)-ketamine during open-heart surgery. *Anesth Analg* 2004; **98:** 1595–1603.
134 Veselis RA, Reinsel RA, Beattie BJ *et al.* Midazolam changes cerebral blood flow in discrete brain regions: an H2(15)O positron emission tomography study. *Anesthesiology* 1997; **87:** 1106–1117.
135 Mathew RJ, Wilson WH, Daniel DG. The effect of nonsedating doses of diazepam on regional cerebral blood flow. *Biol Psychiatry* 1985; **20:** 1109–1116.
136 Forster A, Juge O, Morel D. Effects of midazolam on cerebral blood flow in human volunteers. *Anesthesiology* 1982; **56:** 453–455.
137 Forster A, Juge O, Morel D. Effects of midazolam on cerebral hemodynamics and cerebral vasomotor responsiveness to carbon dioxide. *J Cereb Blood Flow Metab* 1983; **3:** 246–249.
138 Matthew E, Andreason P, Pettigrew K *et al.* Benzodiazepine receptors mediate regional blood flow changes in the living human brain. *Proceedings of the National Academy of Sciences of the United States of America* 1995; **92:** 2775–2779.
139 Knudsen L, Cold GE, Holdgard HO *et al.* The effects of midazolam on cerebral blood flow and oxygen consumption Interaction with nitrous oxide in patients undergoing craniotomy for supratentorial cerebral tumours. *Anaesthesia* 1990; **45:** 1016–1019.
140 Volkow ND, Wang GJ, Hitzemann R *et al.* Depression of thalamic metabolism by lorazepam is associated with sleepiness. *Neuropsychopharmacology* 1995; **12:** 123–132.
141 Wolf J, Friberg L, Jensen J *et al.* The effect of the benzodiazepine antagonist flumazenil on regional cerebral blood flow in human volunteers. *Acta Anaesthesiol Scand* 1990; **34:** 628–631.
142 Forster A, Juge O, Louis M *et al.* Effects of a specific benzodiazepine antagonist (RO 15-1788) on cerebral blood flow. *Anesth Analg* 1987; **66:** 309–313.
143 Chiolero RL, Ravussin P, Anderes JP *et al.* The effects of midazolam reversal by RO 15-1788 on cerebral perfusion pressure in patients with severe head injury. *Intensive Care Med* 1988; **14:** 196–200.
144 Knudsen L, Cold GE, Holdgard HO *et al.* Effects of flumazenil on cerebral blood flow and oxygen consumption after midazolam anaesthesia for craniotomy. *Br J Anaesth* 1991; **67:** 277–280.
145 Harte GJ, Gray PH, Lee TC *et al.* Haemodynamic responses and population pharmacokinetics of midazolam following administration to ventilated, preterm neonates. *J Paediatr Child Health* 1997; **33:** 335–338.
146 Jorch G, Rabe H, Rickers E *et al.* Cerebral blood flow velocity assessed by Doppler technique after intravenous application of diazepam in very low birth weight infants. *Dev Pharmacol Ther* 1989; **14:** 102–107.
147 Van Alfen-van der Velden AA, Hopman JC, Klaessens JH, *et al.* Effects of midazolam and morphine on cerebral oxygenation and hemodynamics in ventilated premature infants. *Biol Neonate* 2006; **90:** 197–202.
148 Abdallah C, Karsli C, Bissonnette B. Fentanyl is more effective than remifentanil at preventing increases in cerebral blood

flow velocity during intubation in children. *Can J Anaesth* 2002; **49:** 1070–1075.
149 Glass PS, Gan TJ, Howell S. A review of the pharmacokinetics and pharmacodynamics of remifentanil. *Anesth Analg* 1999; **89:** S7–14.
150 Guy J, Hindman BJ, Baker KZ *et al.* Comparison of remifentanil and fentanyl in patients undergoing craniotomy for supratentorial space-occupying lesions. *Anesthesiology* 1997; **86:** 514–524.
151 Klimscha W, Ullrich R, Nasel C *et al.* High-dose remifentanil does not impair cerebrovascular carbon dioxide reactivity in healthy male volunteers. *Anesthesiology* 2003; **99:** 834–840.

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