

## Brain perfusion part 2: anesthesia and brain perfusion in small animals

### *Hersenperfusie*

#### *deel 2: anesthesie en hersenperfusie bij kleine huisdieren*

<sup>1</sup>T. Waelbers, <sup>2</sup>K. Peremans, <sup>2</sup>I. Gielen, <sup>2</sup>S. Vermeire, <sup>1</sup>I. Polis

<sup>1</sup> Department of Medicine and Clinical Biology of Small Animals  
Faculty of Veterinary Medicine, University of Ghent

<sup>2</sup> Department of Medical Imaging of Domestic Animals and Small Animal Orthopedics  
Faculty of Veterinary Medicine, University of Ghent  
Salisburylaan 133, 9820 Merelbeke, Belgium

tim.waelbers@UGent.be

#### ABSTRACT

**Sedatives and anesthetics can influence cerebral metabolism and respiratory and cardiovascular dynamics, which results in changes in cerebral perfusion. This is of major importance when functional brain imaging techniques are used to measure cerebral blood flow or to evaluate neurotransmitter systems, and also during neurosurgery. In the present review, the influences on brain perfusion of different sedatives including opioids and anesthetics commonly used in veterinary medicine are summarized.**

#### SAMENVATTING

Sedativa en anestetica kunnen de ventilatie, het cardiovasculaire systeem en het metabolisme van de hersenen beïnvloeden. Dit kan resulteren in veranderingen in de hersendoorbloeding, hetgeen van belang kan zijn wanneer functionele beeldvormingstechnieken gebruikt worden om de hersenperfusie te meten, om neurotransmittersystemen te beoordelen of ook tijdens neurochirurgie. In dit tweede deel over hersenperfusie wordt de invloed van diergeneeskundig regelmatig gebruikte sedativa, opiaten en anestetica op de hersenperfusie besproken.

#### INTRODUCTION

Knowledge of the influences of anesthetics on cerebral blood flow (CBF) and metabolism is an important issue in human medicine, especially for patients with elevated intracranial pressure or who are scheduled for neurosurgery. The main goal of the anesthesiologist in these cases is to prevent the occurrence of secondary brain injuries and cerebral ischemia (Audibert *et al.*, 2005; Van Aken and Van Hemelrijck, 1991). In addition, it is important to be aware of the effect of sedatives or anesthetics on the regional or global brain perfusion when functional brain imaging modalities to assess (regional) cerebral blood flow (rCBF) are applied in veterinary patients (Peremans *et al.*, 2001). Finally, altered cerebral circulation induced by anesthesia can influence the disposability of the radioligands when neurotransmitter systems are evaluated using specific radioligands, as already reported in cats (Hassoun *et al.*, 2003).

Sedatives and anesthetics affect not only the cerebral metabolism, but also the respiratory and cardiovascular dynamics. All these parameters have clear influences on the cerebral blood flow. Consequently, the administration of anesthetics can be accompanied by several, sometimes opposing influences on the cerebral blood flow, whereby the final effect is difficult to

predict. Most anesthetics cause an inhibition of the neuronal activity, resulting in decreased cerebral metabolism, which in turn causes the cerebral vessels to constrict. Simultaneously, these anesthetics can induce hypoventilation, accompanied by hypercapnia, or hypotension. Both hypoventilation and hypotension induce vasodilation or at least blunt the vasoconstriction resulting from the formerly mentioned decreased metabolism. Another concern is the change in cerebral blood flow in a region dependant manner induced by some anesthetic agents (Schlunzen *et al.*, 2006).

Since anesthesia is mandatory in veterinary medicine for procedures where cerebral blood flow is measured, the effects of commonly used sedatives and anesthetics on the cerebral blood flow are reviewed in the present paper.

#### Influence of $\alpha_2$ -agonists

Alpha<sub>2</sub>-agonists induce a reliable dose dependent sedation, analgesia and muscle relaxation, and are widely used in veterinary medicine. The  $\alpha_2$ -receptors are located both in neuronal and also in non-neuronal tissues, including in the vascular endothelium and platelets throughout the body; norepinephrine (NE) is the most important endogenous ligand for these receptors (Kanawati *et al.*, 1986; Tsukahara *et al.*, 1986).

All norepinephrine receptors can be postsynaptic heteroreceptors, but only the  $\alpha_2$ -receptors can act as presynaptic autoreceptors, producing a negative feedback regulatory signal when stimulated. The most important effect of  $\alpha_2$ -receptor stimulation in the central nervous system is an inhibition of the release of NE, resulting in decreased centrally mediated sympathetic activity and sedation (Aghajanian and Vandermaelen, 1982; Bhana *et al.*, 2000; Kamibayashi and Maze, 2000; Lipscombe *et al.*, 1989; Prielipp *et al.*, 2002; Stahl, 2008).

Alpha<sub>2</sub>-agonists cause an initial peripheral vasoconstriction, which leads to increased blood pressure, which in turn causes a reflex bradycardia. The centrally induced decrease of the sympathetic nervous tone also leads to a decreased heart rate and blood pressure. Since hypotension was not reported in clinical studies in dogs, this species might be more sensitive for the vasoconstrictor effects of  $\alpha_2$ -agonists compared to humans (Khan *et al.*, 1999; Lemke, 2007; Murrell and Hellebrekers, 2005; Pypendop and Verstege, 1998).

Overall,  $\alpha_2$ -agonists have cerebral protecting properties as they decrease intracranial pressure (ICP) by reducing cerebral blood volume. Since most of the blood volume is situated in the venous compartment and  $\alpha_2$ -agonists are potent vasopressors on the venous side of the cerebral pial circulation, a decrease in ICP can be expected. However, a possible autoregulatory response can counteract the previously mentioned intrinsic effect of  $\alpha_2$ -agonists on the cerebral perfusion (Iida *et al.*, 1999; Ter Minassian *et al.*, 1997). Systemic administration of  $\alpha_2$ -agonists not only decreases global CBF but also limits hypercapnia- and hypoxia-induced cerebral vasodilation (Fale *et al.*, 1994; McPherson *et al.*, 1994; Zornow *et al.*, 1990).

### *Xylazine*

Administration of xylazine in isoflurane anesthetized rats was reported to induce a region-dependent reduction in CBF (largest reduction in the hypothalamus and septum, smallest reduction in the caudate putamen) (Lei *et al.*, 2001). This reduction in CBF could partly be explained by the well known effects of xylazine on the cardiac output, the respiratory system and the cerebral perfusion pressure, but also by direct effects on central and peripheral  $\alpha_2$ -receptors. Whether the coupling between CBF and the cerebral metabolic rate of oxygen consumption (CMRO<sub>2</sub>), which is a reflection of the oxygen requirements for the brain, remains intact under anesthesia including xylazine was left unclear. In a model of intracranial hypertension in dogs, a significant dose-dependent decrease in ICP after administration of xylazine was also demonstrated (McCormick *et al.*, 1993).

### *Medetomidine and dexmedetomidine*

Although the racemic mixture of medetomidine administered in isoflurane anesthetized dogs was reported to be accompanied by significant increases in

systolic and diastolic pressure, surprisingly this mixture did not significantly change the intracranial pressure (Keegan *et al.*, 1995).

In contrast, dexmedetomidine, which is the S-enantiomer of medetomidine, was reported to induce a significant decrease in CBF in isoflurane or halothane anesthetized dogs. However, this decrease in CBF could not be associated with a significant increase in mean arterial pressure or a change in the cerebral metabolic rate of oxygen (CMRO<sub>2</sub>), most likely because dexmedetomidine was administered as a continuous infusion over 15 minutes. Therefore, the observed CBF decrease was presumably induced by the occurrence of an  $\alpha_2$ -receptor-mediated vasoconstriction. In addition, the possibility of the inhibition of specific brain regions with dense concentrations of  $\alpha_2$ -receptors has also been mentioned (Karlsson *et al.*, 1990; Prielipp *et al.*, 2002; Zornow *et al.*, 1990). The reduction of the volatile anesthetic induced vasodilation by dexmedetomidine was further confirmed in a closed cranial window CBF study in dogs, where the reduction in diameter of pial vessels after the intravenous administration of dexmedetomidine was more striking in arterioles than in venules and was not dose dependent (Ohata *et al.*, 1999). However, cerebral pial venules tended to exhibit more prominent constriction compared to arterioles when dexmedetomidine was administered topically in man, while an opposite effect was noticed in the spinal vessels. As not only the pial vessels but also the intraparenchymal arterioles play a role in the regulation of the CBF, conclusions regarding the CBF cannot be made by observing only the pial vessel diameters (Iida *et al.*, 1999).

Apparently, the vasoconstrictive effects of  $\alpha_2$ -agonists are of greater importance for the cerebral vasculature than the autoregulatory mechanisms, resulting in decreased CBF and ICP.

### **Influence of benzodiazepines**

As benzodiazepines can cause dysphoria and excitation after intravenous administration in small animals, these drugs are seldom used as a sole sedative in these species (Court and Greenblatt, 1992; Covey-Crump and Murison, 2008; Ilkiw *et al.*, 1996; Stegmann and Bester, 2001). However, these drugs are routinely used in combination with other sedatives, injectable anesthetics and ketamine because of their good muscle relaxant effect and limited effects on cardiovascular and pulmonary functions. Benzodiazepines are also frequently used as anticonvulsants (Itamoto *et al.*, 2000; Lemke, 2007).

Benzodiazepines produce most of their pharmacological effects by modulating the  $\gamma$ -aminobutyric acid (GABA)-mediated neurotransmission. GABA is a primary inhibitory neurotransmitter in the mammalian nervous system since cell membranes of most central nervous system neurons express GABA receptors (Tanelian *et al.*, 1993). When benzodiazepines interact with these specific receptors, the GABA-mediated chloride ion conductance is potentiated so the net result is enhancement of GABA-mediated inhibitory

synaptic events. As inhibitory changes in neuron activity of a certain brain region result in decreased regional cerebral blood flow (rCBF) and because of the widespread distribution of GABAergic neurons and their corresponding receptors, changes in rCBF can be seen after the administration of benzodiazepines (Matthew *et al.*, 1995). The administration of benzodiazepines was indeed associated with decreases in rCBF and glucose utilization in an experimental rat study (Kelly *et al.*, 1986). Moreover, different benzodiazepines, including triazolam, midazolam and lorazepam, significantly reduced both CBF and the cerebral metabolic rate in humans, dogs and piglets (Ahmad *et al.*, 2000; Forster *et al.*, 1982; Roald *et al.*, 1986; Yeh *et al.*, 1988). In another human study, this effect was proven to be mediated, at some level, through the benzodiazepine site located on the GABA receptor, since flumazenil, the classic benzodiazepine antagonist, was able to reverse this effect. The largest reductions in rCBF were seen in the thalamus, a region where, surprisingly, the density of benzodiazepine binding sites is the lowest. This finding suggests that benzodiazepines produce changes in the activity of neurons in regions removed from but connected to areas of high binding site density (Matthew *et al.*, 1995).

As benzodiazepines produce only minimal effects on cardiovascular and pulmonary functions in dogs, a change in CBF is not induced by changes in arterial partial pressure of oxygen or carbon dioxide or by fluctuations in blood pressure (Haskins *et al.*, 1986; Hellyer *et al.*, 1991; Jones *et al.*, 1979).

### Influence of opioids

Opioids are frequently used in man and animals in combination with sedatives or anesthetics for their potent analgesic effects. They exert their effect on cerebral hemodynamics mainly through the cardiorespiratory changes that they induce. However, most opioids have minimal effects in animals on cardiac output, cardiac rhythm and arterial blood pressure when clinically relevant analgesic doses are administered (Lamont and Mathews, 2007). The responsiveness of the brain-stem respiratory centers to carbon dioxide, on the other hand, is of importance. Indeed, opioids can decrease this responsiveness, especially during general anesthesia, causing a marked hypercapnia, which results in an increase in CBF (Akca, 2006; Cullen *et al.*, 1999; Lamont and Mathews, 2007).

Another important issue relating to the use of opioids in small animals is the occurrence of hypotension, which can influence cerebral hemodynamics (Bedell *et al.*, 1998; Lamont and Mathews, 2007; Matsumiya and Dohi, 1983; Werner *et al.*, 1992). However, several human studies have confirmed that ICP does not increase after the administration of opioids when CO<sub>2</sub> and blood pressure are kept constant (Albanese *et al.*, 1997; Bazin, 1997; Bourgoin *et al.*, 2005; Paris *et al.*, 1998). Studies in dogs showed a decrease in CBF and CMRO<sub>2</sub>, but a stable or even decreased ICP when morphine, sufentanil or remifentanil were administered during halothane or isoflurane anesthesia (Hoff-

man *et al.*, 1993; Matsumiya and Dohi, 1983; Werner *et al.*, 1992).

In conclusion, CBF remains stable or may possibly decrease after the administration of opioids, on the condition that blood pressure and arterial carbon dioxide tension are kept constant.

### Influence of injectable anesthetics

Most injectable anesthetic drugs used in veterinary medicine (i.e. barbiturates, propofol, etomidate and alfaxalone) alter the transmission mediated by the inhibitory neurotransmitter GABA (GABA<sub>A</sub> more specifically). Prediction of activity and individual drug pharmacology is complicated by the existence of several GABA<sub>A</sub>-receptor subunits and drug-specific differences in GABA<sub>A</sub> activity (Branson, 2007; Lambert *et al.*, 2003; Muir *et al.*, 2009). Overall, barbiturates, propofol, etomidate and alfaxalone decrease neuronal activity, thus decreasing the demand for oxygen by the brain. As metabolism is coupled to CBF, a parallel decrease in CBF occurs, resulting in a decline of ICP (Bazin, 1997; Kaisti *et al.*, 2003; Werner, 1995).

#### Barbiturates

Barbiturates administered at lower concentrations cause a neuronal depression by decreasing the rate of dissociation of GABA from the GABA receptor. However, at higher concentrations they start to activate directly the chloride ion channel associated with the GABA receptors (Dunwiddie *et al.*, 1986; Huidobrotoro *et al.*, 1987; Schwartz *et al.*, 1985). In humans and dogs, barbiturates were reported to produce a 50% reduction in CBF and cerebral metabolism, while cerebrovascular reactivity to carbon dioxide was mostly maintained (Akca, 2006; Kassell *et al.*, 1981). Furthermore, thiopental in humans and pentobarbital in dogs were shown to decrease the CBF, together with a decrease in cerebral oxygen demand (Chin *et al.*, 1983; Pierce *et al.*, 1962).

#### Propofol

Propofol, an injectable anesthetic unrelated to barbiturates, induces depression of the central nervous system by enhancing the effects of the inhibitory neurotransmitter GABA (Concas *et al.*, 1991).

Different studies in healthy human subjects showed reductions in CBF, CMRO<sub>2</sub> and cerebral blood volume (CBV) after the administration of propofol (Byas-Smith *et al.*, 2002; Alkire *et al.*, 1995; Fiset *et al.*, 1999; Kaisti *et al.*, 2003; Vandesteene *et al.*, 1988). The reported reductions in CMRO<sub>2</sub> were greater than the one observed after the administration of thiopental with less cerebral vasoconstriction and reduction of CBF (Newman *et al.*, 1995). These findings were suggestive that propofol might be more justified in relation to the cerebral oxygen supply/demand ratio.

Similar to its effect in man, propofol was reported to decrease CBF and CMRO<sub>2</sub> in dogs with preservation of the vasoconstrictor reflex to hypocapnia. However,

the autoregulation was impaired, but only at high propofol concentrations (Artru *et al.*, 1992). The reduction of CBF was dose dependent until electroencephalogram (EEG) isoelectricity was obtained and was also coupled to a reduced cerebral metabolism. However, when the larger doses required to obtain isoelectricity were administered, no further reduction in cerebral metabolism was observed (Artru *et al.*, 1992). In contrast, exceedingly large doses of propofol in humans can even increase CBF due to the drug's intrinsic vasodilator effect (Akca, 2006). Propofol also decreased the ICP in an experimental model of cerebral edema in cats, (Nimkoff *et al.*, 1997).

Similar to the study by Artru *et al.* (1992) in dogs, cerebral autoregulation and the response to hypercapnia were reported to be maintained in humans. Only the effect of hypocapnia for decreasing CBF may be blunted in patients receiving propofol infusion for the maintenance of anesthesia (Conti *et al.*, 2006; Karsli *et al.*, 2004; Van Aken and Van Hemelrijck, 1991).

### *Etomidate*

The imidazole derivative etomidate appears to work through GABA receptor activation in a similar way as propofol (Blednov *et al.*, 2003; Lingamaneni and Hemmings, 2003; Vanlersberghe and Camu, 2008). Etomidate administered in dogs as a continuous rate infusion induced decreases in CBF and CMRO<sub>2</sub>; the decrease of CMRO<sub>2</sub> continued until the onset of an isoelectric electroencephalogram. The decrease in CBF seemed to be the result of a potent intrinsic vasoconstrictive effect of the drug, as it was not coupled to the decrease in CMRO<sub>2</sub> (Milde *et al.*, 1985).

### *Alfaxalone*

Recently, a new formulation of alfaxalone in a cyclodextran solution has been developed for use in small animals (Alfaxan®, Vétoquinol UK Limited, Buckingham, UK). The effects of this formulation on cerebral hemodynamics are not known. However, because alfaxalone also modulates GABA<sub>A</sub> receptors, and considering the properties of the older alfaxalone-alfadolone combination in cats and humans, a decrease in CBF is most likely to occur after the administration of alfaxalone (Baldy-Moulinier *et al.*, 1975; Bendtsen *et al.*, 1985; Rasmussen *et al.*, 1978; Sari *et al.*, 1976).

In conclusion, all four injectable anesthetic agents decrease the oxygen requirements of the brain sufficiently to provide favorable cerebral protection, although propofol decreases CMRO<sub>2</sub> to a greater extent compared to etomidate or thiopental. As autoregulation is preserved or a specific drug, namely etomidate, has intrinsic cerebral vasoconstrictive effects, CBF is reduced after administration of each of these drugs.

### **Influence of ketamine**

Ketamine is a dissociative anesthetic which interrupts ascending transmission from unconscious to

conscious parts of the brain. There is also evidence of a dissociation between the thalamus and limbic system (Lin, 2007). Antagonism at the N-methyl-D-aspartate (NMDA) receptor has been proposed as the most likely molecular mechanism responsible for the anesthetic and analgesic effects of ketamine.

Ketamine does not cause changes in CMRO<sub>2</sub> and CBF in the whole brain. Only regional increases in CMRO<sub>2</sub>, CBF and glucose utilization have been reported in rats (Cavazzuti *et al.*, 1987; Chi *et al.*, 1994). However, the influence of ketamine on cerebral hemodynamics depends also on the ventilation mode applied during anesthesia. CBF increases in spontaneously breathing human volunteers, but not when ventilation is controlled (Himmelseher and Durieux, 2005). This increase in CBF during spontaneous ventilation was also reported in cats and might be caused by sympathetically induced hypertension related to the occurrence of hypercapnia (Bazin, 1997; Hassoun *et al.*, 2003; Lin, 2007). Increased CBF can also be a direct result of hypercapnia because ketamine only blunts the cerebrovascular reactivity to CO<sub>2</sub> in isoflurane anesthetized humans (Nagase *et al.*, 2001). Ketamine decreased the cerebrovascular reactivity only to some extent and did not block the mechanism completely in spontaneously breathing anaesthetized dogs (Ohata *et al.*, 2001).

The results of studies under controlled ventilation are more conflicting. A significant increase in CBF in ventilated humans after the administration of subanesthetic doses of racemic ketamine as well as of the S-enantiomer of ketamine was reported without changes in CMRO<sub>2</sub> or glucose metabolic rate (Langsjo *et al.*, 2003; Langsjo *et al.*, 2005). Similar results were reported in ventilated rabbits (Oren *et al.*, 1987). On the other hand, ketamine caused a decrease in CMRO<sub>2</sub> with no change in CBF in ventilated goats (Schwedler *et al.*, 1982).

The influence of ketamine on cerebral hemodynamics depends on the combination with other sedative/anesthetic drugs that is used. When ketamine was combined with midazolam in human patients with severe head injury that were being mechanically ventilated (controlled mode), intracranial and cerebral perfusion pressures were maintained to the same extent as when the combination of midazolam with sufentanil was used. However, with the increasing trend to use vasopressors to control arterial pressure in the sufentanil group, more fluids were needed (Bourgoin *et al.*, 2003). Ketamine was even associated with a significant decrease in ICP when a propofol infusion was used in ventilated patients (Albanese *et al.*, 1997). On the other hand, ketamine may increase CBF in the presence of nitrous oxide in man, even under controlled ventilation (Takeshita *et al.*, 1972). Although ketamine reduced the isoflurane induced cerebral vasodilation during isoflurane anesthesia in rabbits, an increase or no change in CBF was reported in humans when ketamine was added to isoflurane anesthesia (Mayberg *et al.*, 1995; Nagase *et al.*, 2003; Strebel *et al.*, 1995). Moreover, neither topical nor systemic administration of ketamine induced changes in pial arteriolar diameter in dogs anes-

thetized with pentobarbital or isoflurane (Ohata *et al.*, 2001).

Apparently, several factors such as the dosage of ketamine, the ventilation method, the presence of background anesthesia and species differences contribute to the differences observed. Consequently, ketamine causes an increase rather than a decrease in CBF, probably because ketamine does not induce a generalized suppression of the brain metabolism. Additionally, the possibility of regional changes has been mentioned by several authors.

### Influence of nitrous oxide (N<sub>2</sub>O)

Although N<sub>2</sub>O has clear analgesic properties, it is not an anesthetic agent for sole use in man or animals, as it is not potent enough to anesthetize a fit, healthy individual. Since the potency of N<sub>2</sub>O in animals is only about half that which has been established in humans, N<sub>2</sub>O in veterinary clinical practice is primarily an anesthetic adjuvant (Steffey and Mama, 2007).

N<sub>2</sub>O was reported to induce an increased CBF in people and goats when used alone (30% to 70% inspiratory concentration) (Aono *et al.*, 1999; Field *et al.*, 1993; Pelligrino *et al.*, 1984). In combination with sevoflurane (1 MAC) or propofol, nitrous oxide also increases cerebral blood flow velocity in healthy children (Rowney *et al.*, 2004; Wilson-Smith *et al.*, 2003). Similarly, inhalation of nitrous oxide caused increases in CBV, CMRO<sub>2</sub> and CBF in dogs (Archer *et al.*, 1987; Theye and Michenfe, 1968).

Nitrous oxide either has a direct effect on the cerebral vessels or it activates certain brain regions, resulting in an increased CMRO<sub>2</sub> (Hancock *et al.*, 2005; Matta and Lam, 1995; Theye and Michenfe, 1968). Interestingly, studies in both humans and goats showed regional differences of the effect of nitrous oxide on the CBF (Lorenz *et al.*, 2001; Pelligrino *et al.*, 1984). In humans, no effect on the dynamic cerebrovascular response to arterial CO<sub>2</sub> changes were observed; cerebral autoregulation, however, was impaired when N<sub>2</sub>O was administered without additional anesthetics (Audibert *et al.*, 2005; Girling *et al.*, 1999). Unfortunately, studies of these specific issues are not available in small animals.

### Influence of volatile anesthetics

Volatile anesthetics generally increase CBF in a dose-dependent manner, while progressively depressing cerebral metabolism, thereby challenging the classic "neuronal activity  $\approx$  metabolism  $\approx$  blood flow" paradigm (Kaisti *et al.*, 2003; Mielck *et al.*, 1999). The disproportion between brain perfusion and metabolism becomes obvious when the CBF/CMRO<sub>2</sub> ratio is calculated. All volatile anesthetics cause an increase of this ratio both in humans and in dogs. The increase is more pronounced when isoflurane is used, compared to halothane and sevoflurane. These differences are most likely induced by the weaker vasodilating effect of sevoflurane, whereas some have suggested that the metabolism is decreased less when halothane is used

(Algotsson *et al.*, 1988; Hansen *et al.*, 1989; Kuroda *et al.*, 1996; Oshima *et al.*, 2003; Scheller *et al.*, 1990). Since not all volatile anesthetics suppress the brain metabolism to the same extent, this difference has been accepted as another confounding factor resulting in the recorded CBF alterations.

Volatile anesthetics have both a direct intrinsic dilating effect on cerebral vessels and an indirect extrinsic constricting effect related to the depression of the brain metabolism (Hans and Bonhomme, 2006; Ogawa *et al.*, 1997). Consequently, the decrease in cerebral blood flow due to the decreased cerebral metabolism is less than expected because of this direct vasodilating effect. The intrinsic vasodilating effect is dose dependent and more pronounced for halothane and desflurane compared to isoflurane and sevoflurane (De Deyne *et al.*, 2004; Hansen *et al.*, 1989; Kuroda *et al.*, 1996; Matta and Lam, 1995; Matta *et al.*, 1999; Ogawa *et al.*, 1997). The weaker intrinsic vasodilatory action of sevoflurane also explains the well maintained cerebral autoregulation and cerebrovascular CO<sub>2</sub> reactivity, as well as the constant intracranial pressure, in both Sevoflurane anesthetized humans and dogs (Artru *et al.*, 1997; Cho *et al.*, 1996; Gupta *et al.*, 1997; Takahashi *et al.*, 1993). These characteristics make sevoflurane the volatile anesthetic of choice for brain compromised patients.

In an awake patient or during a light plane of anesthesia where CMR is high, the reduction in CMR caused by the volatile anesthetic produces a decrease in CBF (Summors *et al.*, 1999). However, if the CMR is already low, CBF increases by direct vasodilation. Therefore, flow-metabolism coupling is preserved at low concentrations of isoflurane and sevoflurane, and the net effect is a reduction in CBF. When high concentrations of both volatiles are used, CBF increases with a loss of cerebral autoregulation. This conclusion is supported by the observation of a reduction of CBF during the administration of sevo- and desflurane, compared to the awake state, both in man and in dogs (Mielck *et al.*, 1998; Mielck *et al.*, 1999). Halothane seems to be an exception as, at least in cats, CBF is assumed to increase compared to the awake state when using this volatile anesthetic (Hassoun *et al.*, 2003).

In humans, volatile anesthetics produce not only global but also regional CBF alterations due to different effects on the anterior and posterior circulation. The location and the magnitude of these flow alterations depend on the kind of anesthetic and its concentration (Kaisti *et al.*, 2003; Reinstrup *et al.*, 1995; Schlunzen *et al.*, 2006; Schlunzen *et al.*, 2004).

Besides the ability to change the tone of the cerebral resistance vessels, volatile anesthetics can also influence autoregulation, again in an anesthetic- and dose-dependent manner (De Deyne *et al.*, 2004; Miletich *et al.*, 1976; Morita *et al.*, 1977). When high doses of volatile anesthetics are administered, the cerebral vessels are already maximally dilated and therefore cannot further compensate when the systemic blood pressure decreases. In humans, it is generally accepted that cerebrovascular autoregulation is maintained up to 1.5 MAC, but becomes progressively impaired at higher

concentrations (Akca, 2006; De Deyne *et al.*, 2004; Gupta *et al.*, 1997; Summors *et al.*, 1999).

The response to CO<sub>2</sub>, as such, is more or less maintained during the administration of volatile anesthetics. There are two mechanisms altering the tone of the cerebral vessels, and mutual interference occurs between them. In rats, for example, hypercapnia increases CBF less during isoflurane anesthesia than in the awake animal (Sicard *et al.*, 2003). Also in dogs and cats, the vasoconstriction of the cerebral vasculature, induced by hypocapnia, is maintained during different levels of isoflurane anesthesia, whereas the vasodilation response to hypercarbia is impaired, but only at higher isoflurane concentrations (Drummond and Todd, 1985; McPherson *et al.*, 1989). Halothane, however, attenuated the hypocapnia-induced vasoconstriction to a larger extent than isoflurane or sevoflurane in an *in vitro* study on isolated dog cerebral arteries (Ogawa *et al.*, 1997).

The data in the literature on the effects on the CBF of all volatile anesthetics in general, and of isoflurane in particular, are not consistent. Because of counteracting mechanisms, dose dependency, concurrent administration of other anesthetics, the influence of nociception in surgical studies, different measurement methods and possible species differences, the results obtained are often difficult to compare. A distinction has to be made when comparing volatile anesthetics to one another or when comparing the awake state to anesthetic conditions. Another important factor is the duration of administration of the volatile agent, as CBF has been reported to decrease over time in isoflurane anesthetized dogs (Brian *et al.*, 1990; McPherson *et al.*, 1991). An overview of the effects of volatile anesthetics on brain perfusion and metabolism is provided in Table 1.

## CONCLUSION

A review of the literature on the effects of anesthesia on the cerebral hemodynamics reveals that every single sedative or anesthetic drug has a clear effect. These products affect cerebral perfusion not only by changing the tone of the cerebral vessels themselves, but also by changing the cerebral metabolism. These effects have important consequences for the regulation of CBF during brain surgery. Moreover, when evaluating brain perfusion with imaging modalities, the use of different anesthetic protocols may result in unreliable results. Especially in situations where regional cerebral blood flows are compared, anesthetic induced regional blood flow changes should be avoided and anesthetics causing only global changes should be preferred. The use of anesthetics results in regional blood flow changes possibly causing significant alterations of distribution of the ligand in specialized neuroreceptor ligand studies. To be able to compare different brain regions at a specific moment or to compare specific measurements in the same animal at different time points, it is justified to avoid anesthetics causing rCBF changes. Moreover, the use of a standardized dosage is extremely important for these procedures.

Because changes in CBF can also occur as a result of changes in arterial oxygen and carbon dioxide tensions and of blood pressure, all of which are influenced by the level of anesthesia, the results are not easy to predict. Therefore these secondary changes should be minimized by keeping the blood pressure and the arterial oxygen and carbon dioxide tensions within physiological ranges, thereby reducing the influence of the anesthesia on the cerebral hemodynamics.

**Table 1. Effects of volatile anesthetics on brain perfusion and metabolism.**

Anesthetic	Species	CBF	CMRO <sub>2</sub>	Vmca	Compared to	Reference
Halothane	Cat	↑			Awake	Hassoun <i>et al.</i> 2003
Halothane	Cat	↑	↓		N <sub>2</sub> O+O <sub>2</sub>	Todd and Drummond, 1984
Halothane	Man	↑			Isoflurane	Young <i>et al.</i> 1989
Halothane	Baboon	↓→↑	↓		Phencyclidine+N <sub>2</sub> O	Brüssel <i>et al.</i> 1991
Halothane	Man	↑	↑		Fentanyl+N <sub>2</sub> O	Algotsson <i>et al.</i> , 1988
Sevoflurane	Man			↓	Sufentanil+N <sub>2</sub> O	Artru <i>et al.</i> 1997
Sevoflurane	Man	↑	↓		Midazolam+fentanyl	Oshima <i>et al.</i> 2003
Sevoflurane	Man			↓	Awake	Cho <i>et al.</i> 1996
Sevoflurane	Man			↓	Awake	Conti <i>et al.</i> 2006
Sevoflurane	Man			↓	Awake	Gupta <i>et al.</i> 1997
Sevoflurane	Man	↓	↓		Awake	Mielck <i>et al.</i> 1999
Desflurane	Dog	↑			Desflurane (lower concentration)	Lutz <i>et al.</i> 1990
Desflurane	Man	↓	↓		Awake	Mielck <i>et al.</i> 1998
Desflurane	Pig	↑			Isoflurane	Holmström and Akeson, 2003
Desflurane	Dog	↓			Desflurane (lower concentration)	Milde and Milde 1991
Isoflurane	Cat	↔	↓		N <sub>2</sub> O+O <sub>2</sub>	Todd and Drummond, 1984
Isoflurane	Man	↑	↓		Midazolam+fentanyl	Oshima <i>et al.</i> 2003
Isoflurane	Man	↔	↓		Fentanyl+N <sub>2</sub> O	Algotsson <i>et al.</i> , 1988
Isoflurane	Man			↓	Sufentanil+N <sub>2</sub> O	Artru <i>et al.</i> 1997
Isoflurane	Dog		↓	↓	Isoflurane (lower concentration)	Zornow <i>et al.</i> 1990

CMRO<sub>2</sub>: cerebral metabolic rate of oxygen consumption

CBF: cerebral blood flow

Vmca: middle cerebral artery flow velocity

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