

## The effects of general anesthesia and variations in hemodynamics on cerebral perfusion

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Applied Cardiopulmonary Pathophysiology 13: 157-159, 2009

Perioperative stroke and ischemic neurological deficits frequently occur following surgical interventions. While stroke may be present following general surgery or resection of head and neck tumors, the incidence in severity of stroke is particularly dramatic in patients subjected to carotid endarterectomy, combined CABG and valve surgery and aortic repair [7]. Since stroke is an obvious perioperative complication and challenge it is important to entirely understand perioperative cerebral perfusion. As one segment of this understanding an analysis of the anesthetic effects on cerebral perfusion is mandatory. This review focuses on the effects of anesthetic agents on parameters of cerebral perfusion such as

- a) vasodilation, vasoconstriction
- b) cerebral perfusion pressure
- c) cerebrovascular autoregulation
- d) CO<sub>2</sub>-reactivity

### **Vasodilation, vasoconstriction**

Studies in laboratory animals and humans have shown that hypnotic agents such as propofol and thiopental produce vasoconstriction in brain vessels. While the overall vasoconstriction is similar between both agents, propofol vasoconstricts more frontal and brainstem territories while thiopental is predominantly vasoconstricting in occipital brain territory [8]. In-vitro preparation of bovine arterial segments have shown that hypnotic agents, particularly propofol, is a vasodilator by blocking sodium and calcium channels. Thus it is intriguing that in-vivo preparations demonstrate hypnotic agents to be vasoconstrictive. The underlying mechanism of hypnotic induced vasoconstriction is the concomitant decrease in cerebral metabolism. Studies in volunteers and patients have

shown that propofol decreases cerebral metabolism with a consecutive decrease in cerebral blood flow (i.e. vasoconstriction) [3]. This demonstrates that the intrinsic (direct) vasodilation as induced by propofol is overridden by cerebral metabolic depression with a consecutive decrease in cerebral blood flow. Similarly, sevoflurane, a volatile anesthetic agent, decreases cerebral blood flow secondary to decreases in cerebral metabolism at concentrations less than 1 MAC [3]. This effect seems unique for volatile anesthetic agents since in-vitro and in-vivo experiments have previously shown that halothane, desflurane and isoflurane are potent vasodilators which increase cerebral blood flow despite the fact that they decrease cerebral metabolism. Because cerebral blood flow and metabolism are reduced in the presence of propofol, barbiturates and sevoflurane coupling between cerebral blood flow and metabolism is intact. However, since halothane, isoflurane and desflurane increase flow but decrease metabolism, the classical approach of flow metabolism coupling is impaired with these compounds. Similar to vasodilating volatile anesthetic agents nitrous oxide is a potent cerebral vasodilator [6]. The vasodilating potency of nitrous oxide is profound and can not be entirely antagonized by concomitant hypocapnia. Ketamine, a non-competitive NMDA-receptor antagonist, has been recently proposed as an analgetic/antinociceptive agent with favourable characteristics for patients undergoing cardiovascular surgery. Ketamine induces regional specific vasodilation and in line with the dissociative concept of mechanism increases and decreases cerebral metabolism in distinct brain regions [4]. This indicates that ketamine is a direct cerebral vasodilator irrespective of cerebral metabolic demands. Dexmedetomidine, an  $\alpha_2$ -adrenergic agonist, possesses vasoconstrictive potential. Studies in humans demonstrate a generalized decrease in cerebral blood

flow [5]. However, this is not entirely matched with decreases in cerebral metabolism, suggesting that dexmedetomidine possesses direct vasoconstrictive potential.

### Cerebral perfusion pressure

Cerebral perfusion pressure (CPP) is determined by the difference between mean arterial blood pressure (MAP) and intracranial pressure (ICP). Therefore and in order to interpret anesthetic effects on CPP their effects on MAP and ICP must be considered. In general anesthetic agents (barbiturates, propofol, benzodiazepines, opioids, dexmedetomidine, sevoflurane, desflurane and isoflurane) decrease MAP in a dose dependent fashion. Likewise, their potential to decrease systemic hemodynamics is related to the speed of application and the pre-existing volume status of the patient. The only drug with stimulating potential on systemic hemodynamics is ketamine. In contrast, barbiturates and propofol decrease ICP with benzodiazepines, ketamine, dexmedetomidine and sevoflurane (< 1 MAC) little to no impact on ICP. Due to their potent vasodilatory stimulation desflurane, isoflurane and nitrous oxide increase ICP due to increases in cerebral blood volume. Therefore, and in balance of effects on MAP and ICP, barbiturates and propofol may increase CPP if the administration is not associated with the decrease in MAP but only with a decrease in ICP. While benzodiazepines and narcotic agents have little to no effect on CPP because of their net zero effects on MAP and ICP, ketamine increases cerebral perfusion pressure. Dexmedetomidine, desflurane and isoflurane decrease CPP because they either decrease MAP or do both decrease MAP and increase ICP.

### Cerebrovascular autoregulation

Cerebrovascular autoregulation refers to the ability of brain vessels to vasoconstrict and vasodilate within a wide range of CPP. If CPP increases, cerebrovascular constriction occurs with the effect of decreasing cerebral blood volume and constant cerebral blood flow. Similarly, increases in CPP induce autoregulatory vasodilation, increase cerebral blood volume and maintain cerebral blood flow constant. In case of impaired cerebral blood flow autoregulation changes in cerebral blood flow occur in a pressure passive fashion with an inverse effect on cerebral volume. That is with increas-

ing CPP cerebral blood volume increases because the vessels get passively dilated and with decreasing CPP there is vascular collapse and decreases in flow and blood volume. Studies in laboratory animals and humans have shown, that intravenous anesthetic agents (hypnotics, ketamine, narcotic agents) maintain cerebral blood flow autoregulation [2]. In contrast, drugs with vasodilating potential such as desflurane and high-dose sevoflurane impair dynamic and static autoregulatory responses [1,9].

### CO<sub>2</sub>-reactivity

CO<sub>2</sub>-reactivity refers to the ability of brain vessels to vasoconstrict in the presence of hypocapnia and to vasodilate in the presence of hypercapnia. This important physiological regulatory response should not be impaired by anesthetic agents. Fortunately, all anesthetic agents irrespective of the vasoconstrictive or vasodilative potential maintain CO<sub>2</sub>-reactivity. While the slope in response may be different, the overall quality of maintenance of this regulation is not impaired.

### Conclusion

Anesthetic agents have direct and indirect action on brain vessels. While they may induce vasodilation *in vitro* (i.e. propofol), they may vasoconstrict within the full biological system.

Figure 1 summarizes the effects of anesthetic agents on vasodilation and vasoconstriction and associated determinants such as CPP, cerebrovascular autoregulation and CO<sub>2</sub>-reactivity. Based on this analysis it is important to understand that anesthetic agents always affect cerebrovascular tone, metabolism, perfusion pressure and autoregulation in a drug specific fashion. Thus, the knowledge of anesthetic effects on these physiological variables is essential in the choice of drug for the individual patient. However, and within the setting of cardiac surgery and cardiopulmonary bypass cerebral perfusion will be additionally determined by factors such as pump flow, pressure on pump, choice of temperature and selection of acid base management.

	Dilation/Constriction of cerebral vessels	CPP	Cerebrovascular autoregulation	CO <sub>2</sub> -reactivity
propofol	vasoconstriction	↑↓	intact	intact
thiopental	vasoconstriction	↑↓	intact	intact
desflurane	vasodilation	↓	impaired	intact
isoflurane	vasodilation	↓	impaired	intact
sevoflurane	(vasodilation)	(↓)	(impaired)	intact
ketamine	vasodilation	↑	intact	intact
dexmedetomidine	vasoconstriction	↓	intact	intact

Figure 1. Effects of anesthetic agents on vasodilation/-constriction and associated determinants such as cerebral perfusion pressure (CPP), cerebrovascular autoregulation and CO<sub>2</sub>-reactivity.

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