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The Response of the Canine Cerebral Circulation to Hyperventilation during Anesthesia with Desflurane

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Arterial CO_2 tension (Pa_{CO_2}) is an important factor controlling cerebral blood flow (CBF) and cerebral vascular resistance (CVR) in animals and humans. The normal responsiveness of the cerebral vasculature to Pa_{CO_2} is approximately 2 ml · min^{-1} · 100 g^{-1} · mmHg^{-1}. This study examined the effect of desflurane, a new volatile anesthetic, on the responsiveness of the cerebral vasculature to changes in Pa_{CO_2}. Mean arterial pressure (MAP), CBF, CVR, intracranial pressure (ICP), and cerebral metabolic rate for O_2 (CMR_{O_2}) were measured in five dogs anesthetized with desflurane (0.5–1.5 MAC) at normocapnia (Pa_{CO_2} = 40 mmHg) and at two levels of hypocapnia (Pa_{CO_2} = ~30 and ~20 mmHg). Under desflurane anesthesia, similar changes in CBF and CVR occurred with hyperventilation at all MAC levels of desflurane. At 0.5 MAC, CBF decreased significantly, from 81 ± 6 to 40 ± 3 ml · min^{-1} · 100 g^{-1} ($P < 0.05$, mean ± SE) when Pa_{CO_2} was decreased from 40 to 24 mmHg; *i.e.*, the CBF decreased approximately 2.6 ml · min^{-1} · 100 g^{-1} · mmHg^{-1}. At 1.0 MAC desflurane, CBF decreased significantly, from 79 ± 10 to 43 ± 5 ml · min^{-1} · 100 g^{-1} with hyperventilation (2.0 ml · min^{-1} · 100 g^{-1} · mmHg^{-1}); at 1.5 MAC desflurane, CBF decreased from 65 ± 6 to 38 ± 2 ml · min^{-1} · 100 g^{-1} with hyperventilation (1.6 ml · min^{-1} · 100 g^{-1} · mmHg^{-1}). Despite the significant decreases in CBF with hyperventilation, there was no significant change in ICP. Dose-dependent decreases in MAP were observed with increasing concentrations of desflurane but were not significantly affected by ventilation. It can be concluded that the cerebral vasculature remained responsive to changes in Pa_{CO_2} at all concentrations of desflurane studied, even in the presence of moderate hypotension. (Key words: Anesthetics, volatile: desflurane; I-653. Brain: blood flow; CO_2 response; intracranial pressure. Carbon dioxide: hypocapnia; normocapnia.)

IT IS WELL ESTABLISHED that arterial CO_2 tension (Pa_{CO_2}) is an important factor in controlling cerebral vascular resistance (CVR) and cerebral blood flow (CBF) in healthy animals and humans. An acute increase in Pa_{CO_2} causes a decrease in CVR, which increases the CBF; a decrease in Pa_{CO_2} has the opposite effect.[1] The decrease in CBF that occurs with hypocapnia is an important technique used in neuroanesthesia and in neurologic patients with decreased intracranial elastance. Therefore, the effect of anesthetic agents on the CO_2 responsiveness of the cerebral circulation may influence anesthetic selection in these patients.

It has been demonstrated that the potent vasoconstrictor effect of hypocapnia persists despite the vasodilating effects of halothane and isoflurane.[2,3] The effects of desflurane on the responsiveness of the cerebral vasculature to changes in Pa_{CO_2} have not been examined. The current study was designed to examine the effects of normocapnia and two levels of hypocapnia on CBF, CVR, and intracranial pressure (ICP) at clinically relevant concentrations of desflurane in dogs.

Materials and Methods

This study was approved by the Animal Care and Use Committee at the Mayo Clinic and was performed in five adult fasted beagle dogs weighing 8.5–11.0 kg. Anesthesia was induced with halothane and O_2 while the animals were in an air-tight chamber. Once anesthetized, the animals were removed from the chamber and given pancuronium 0.1 mg · kg^{-1} intravenously *via* a peripheral vein to facilitate tracheal intubation. This dose was repeated hourly to facilitate ventilation with a Harvard® pump, which was adjusted to maintain normocapnia (Pa_{CO_2} = 40 ± 1 mmHg and Pa_{O_2} = 140 ± 10 mmHg). Desflurane at a concentration of 1.5 MAC (10.5%)[4] was administered with a DM-5000 vaporizer modified by Ohmeda to deliver desflurane. Normal saline was administered as maintenance fluid at a rate of 10–15 ml · min^{-1} · 100 g^{-1} into a peripheral vein.

The animal was placed in a sphinx position with the head resting on a block elevated 10 cm above the heart. Cannulae were inserted by cutdown into a femoral artery for measurement of mean arterial pressure (MAP) and blood sampling, and into a femoral vein for return of blood from the superior sagittal sinus diverted for the CBF measurement. A parietal epidural thermistor probe was placed to monitor brain temperature and was maintained at 37 ± 0.1°C with heating pads and lamps. Peripheral electrocardiogram (ECG) needle electrodes were placed for continuous measurement of ECG and heart rate (HR). Biparietal electroencephalogram (EEG) was recorded continuously from four disc electrodes cemented directly to the skull to minimize muscle artifact. A fiberoptic ICP measuring device (P-1500, Ladd Research Industries, Burlington, VT) was inserted superficial to the dura into the parietal epidural space.

Heparin was injected (300–400 IU/kg intravenously), and then the sagittal sinus was exposed, isolated, and cannulated as previously described[5] for direct measurement of CBF in milliliters per minute by a square wave electromagnetic flowmeter (EP 300 API, Carolina Medical Elec-

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tronics).[6] The sagittal sinus drains primarily the anterior, superior, and lateral portions of the cerebral hemispheres, which constitute approximately 54% of the total brain weight.[7] This flow then was adjusted for 100 g brain weight. The cranium then was rigidly sealed with Surgicel® and Vigor/Aron/Alpha® rapid bonding adhesive. At the end of the surgical preparation, the animals' ear canals were occluded and eyes were covered to avoid extraneous stimulation at low MAC levels, and 0.25% bupivacaine was infiltrated into all wound margins.

Arterial blood gas (ABG) and sagittal sinus blood gas values were measured by standard electrodes (model 1303, Instrumentation Laboratories). Blood O_2 content was calculated from measurement of hemoglobin and oxyhemoglobin saturation (model 282, Instrumentation Laboratories).[8] The cerebral metabolic rate for O_2 (CMR_{O_2}) was calculated as the product of CBF and the arterial − sagittal sinus blood O_2 content difference. Cerebral perfusion pressure (CPP) was calculated as the difference between MAP at the head level and ICP. CVR was calculated as an index (CVRI) equal to the quotient of CPP and CBF (per 100 g brain weight). Blood glucose and lactate were measured by an enzymatic technique (glucose oxidase or lactate oxidase) with a glucose analyzer (model 23A, Yellow Springs Instrument). Inspired and end-expired desflurane concentrations were monitored continuously by an infrared analyzer (model 254, Datex, Puritan Bennett) calibrated for desflurane.

Three levels of Pa_{CO_2} were studied (20, 30, and 40 mmHg) at each of three clinically relevant MAC concentrations (0.5, 1.0, and 1.5) of desflurane. To simulate the clinical situation, Pa_{CO_2} was altered by changing the ventilator settings. The order in which the MAC concentrations were studied was randomized. In addition, within a given MAC concentration, the order in which the CO_2 levels were studied was randomized to eliminate any effect of time on the measurements. Each study period consisted of 10 min of equilibration at a given MAC level and a given Pa_{CO_2} level followed by a period of measurements, which were obtained in triplicate. At each MAC level and Pa_{CO_2}, measurements were made of HR, MAP, CBF, CMR_{O_2}, ICP, CVRI, EEG, ABG, and blood glucose and lactate.

For each concentration of desflurane, values were compared at each Pa_{CO_2} level by two-way analysis of variance for repeated measures. When differences were found, significance was tested by Tukey's test for multiple comparisons of paired data.

Results

End-tidal anesthetic concentrations of desflurane were as follows: 0.5 MAC = 3.6 ± 0.1%, 1.0 MAC = 7.0 ± 0.2%, and 1.5 MAC = 10.6 ± 0.4%.[4]

The effect of Pa_{CO_2} on CBF at the three desflurane concentrations are presented in table 1. At all desflurane concentrations, increasing hypocapnia produced a progressive decrease in CBF. At 0.5 MAC desflurane, CBF decreased significantly from 81 ± 6 to 40 ± 3 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ when Pa_{CO_2} was decreased from 40 ± 1 to 24 ± 1 mmHg ($P < 0.05$). This is equivalent to a decrease in CBF of 2.6 $ml \cdot min^{-1} \cdot 100\ g^{-1} \cdot mmHg^{-1}$. At 1.0 MAC desflurane, the CBF decreased from 79 ± 10 to 43 ± 5 $ml \cdot min^{-1} \cdot 100\ g^{-1}$, a change of 2.0 $ml \cdot min^{-1} \cdot 100\ g^{-1} \cdot mmHg^{-1}$. At 1.5 MAC desflurane, the CBF decreased from 65 ± 6 to 38 ± 2 $ml \cdot min^{-1} \cdot 100\ g^{-1}$, a change of 1.6 $ml \cdot min^{-1} \cdot 100\ g^{-1} \cdot mmHg^{-1}$.

The decreases in CBF occurring with hyperventilation at all desflurane concentrations were accompanied by increases in CVRI (Table 1), although the changes did not reach statistical significance by Tukey's test.

Hyperventilation had no significant effect on: CMR_{O_2}; arterial oxygenation, which remained within the range of Pa_{O_2} from 130–160 mmHg; hemoglobin, which ranged from 11.8 to 14.2 g/dl; blood glucose, which ranged from 91 to 102 mg/dl; or blood lactate, which ranged from 2.1 to 2.8 μmol/ml. Hyperventilation produced the expected respiratory alkalosis, such that *p*H

TABLE 1. The Effects of Desflurane and Hyperventilation on Cerebral Hemodynamics

Desflurane (MAC)	Pa_{CO_2} (mmHg)	*p*H	CBF ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	CVRI ($mmHg \cdot ml^{-1} \cdot min \cdot 100\ g$)	ICP (mmHg)	MAP (mmHg)
0.5	40 ± 1	7.34 ± 0.01	81 ± 6	1.33 ± 0.20	13 ± 2	127 ± 7
	32 ± 0*	7.41 ± 0.01*	54 ± 3*	1.94 ± 0.26	9 ± 1	122 ± 6
	24 ± 1*†	7.51 ± 0.01*	40 ± 3*	2.47 ± 0.40	10 ± 1	113 ± 7
1.0	40 ± 1	7.32 ± 0.01	79 ± 10	0.63 ± 0.03	14 ± 3	74 ± 4
	31 ± 1*	7.40 ± 0.01*	70 ± 6	0.75 ± 0.07	17 ± 3	78 ± 6
	22 ± 1*†	7.52 ± 0.01*†	43 ± 5*†	1.59 ± 0.35	11 ± 2	83 ± 9
1.5	40 ± 0	7.31 ± 0.02	65 ± 6	0.60 ± 0.06	15 ± 3	63 ± 3
	31 ± 1	7.39 ± 0.02	45 ± 2	0.82 ± 0.09	13 ± 1	60 ± 4
	23 ± 1	7.50 ± 0.04	38 ± 2	1.05 ± 0.25	11 ± 1	60 ± 9

Values are mean ± SE; n = 5.
* Significantly different from value at P_{CO_2} = 40 ($P < 0.05$).
† Significantly different from value at P_{CO_2} = 30 ($P < 0.05$).

CBF = cerebral blood flow; CVRI = cerebral vascular resistance index; ICP = intracranial pressure; MAP = mean arterial pressure.

was significantly increased at both hypocapnic levels (table 1).

Discussion

Previous studies have reported that the CO_2 responsiveness of the cerebral circulation is preserved during halothane[9] and isoflurane anesthesia[10,11] and may even be enhanced with isoflurane when compared to the CO_2 responsiveness in an awake state or during anesthetic regimens not including volatile agents.[9,12] Drummond and Todd[9] examined CBF responses to Pa_{CO_2} in cats and reported an enhanced response of the cerebral vasculature to Pa_{CO_2} during 1.0 MAC isoflurane/N_2O anesthesia as compared with that during morphine/N_2O anesthesia. In other words, the decrease in CBF with hyperventilation was greater during isoflurane/N_2O anesthesia than during halothane/N_2O or morphine/N_2O anesthesia. However, N_2O, a known cerebral vasodilator,[13] may have influenced the comparative conclusions of that study.

The results of the current study indicate that the cerebral vasculature remains responsive to changes in Pa_{CO_2} throughout the range of desflurane concentrations studied (0.5–1.5 MAC desflurane) and are similar to those present during isoflurane anesthesia. McPherson *et al.*[11] studied the cerebrovascular responsiveness to Pa_{CO_2} in dogs during 1 and 2 MAC isoflurane anesthesia and found that CBF decreased to 40% of normocapnic control when the animals were hyperventilated to a Pa_{CO_2} of 25 mmHg, while CVR increased two-fold. At 0.5 MAC desflurane, a progressive 50% decrease in CBF was evident with hyperventilation. This response remained intact even at 1.5 MAC desflurane: hyperventilation to a Pa_{CO_2} of 23 mmHg reduced CBF by 40%. This reduction in CBF occurred because of an approximate two-fold increase in CVR with hyperventilation at all desflurane concentrations.

The ICP measured at normocapnia ranged from 13–15 mmHg with the three concentrations of desflurane, a result similar to that obtained with desflurane anesthesia in a previous study[14] and to that obtained with isoflurane.[15] This ICP is significantly higher than that measured in the same animal model during anesthesia with the short-acting opioids; in those studies, ICP ranged from 3–7 mmHg,[16,17] indicating that desflurane does increase ICP at normocapnia. Despite the changes in CBF produced by hypocapnia in the current study, ICP did not change significantly. These results are similar to those reported for isoflurane by McPherson *et al.*[11] They reported that despite a 60% decrease in CBF and a two-fold increase in CVR with hyperventilation, ICP (measured as cerebrospinal fluid pressure) did not significantly change.

The lack of an observed effect of hyperventilation on ICP during desflurane anesthesia in the current study may be due to a variety of causes. Although CBF and cerebral blood volume (CBV) change in parallel in response to an anesthetic agent or to changes in Pa_{CO_2}, the slope of the response curve is much less for CBV than for CBF.[18–22] Because it is CBV that primarily affects ICP in the presence of normal intracranial compliance, it cannot be concluded that an observed change in CBF secondary to hyperventilation results in an effect of equal magnitude on CBV or ICP. The observations of the current study were made in dogs with normal intracranial compliance. From this model, it cannot be predicted whether hyperventilation decreases ICP in patients with decreased intracranial compliance during desflurane anesthesia.

In the presence of moderate hypotension (MAP = 60 mmHg) produced by 1.5 MAC desflurane, the CO_2 responsiveness of the circulation was similar in magnitude to that observed at 0.5 MAC (Table 1). Therefore, it appears that CO_2 responsiveness remains intact to the lower limit of autoregulation with desflurane. By comparison, in a similar model, CO_2 responsiveness was reduced by 50% at a MAP of 50 mmHg with isoflurane.[23] However, in that study, the MAP of 50 mmHg may have been below the lower limit of autoregulation and so may have influenced the CO_2 responsiveness.

In summary, the canine cerebral vasculature remained responsive to decreases in Pa_{CO_2} at all clinically relevant concentrations of desflurane studied, even in the presence of moderate hypotension.

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