Cerebrovascular Responsiveness to Carbon Dioxide in Dogs with 1.4% and 2.8% Isoflurane

Robert W. McPherson, M.D.,* Johnny E. Brian, Jr., M.D.,† Richard J. Traysman, Ph.D.‡

Cerebral blood flow (CBF) responsiveness to alterations in arterial CO₂ tensions (PₐCO₂) during 1.4% and 2.8% isoflurane anesthesia was assessed. Dogs were initially anesthetized with thiopental (12 mg/kg, iv bolus), their tracheae intubated, after which anesthesia was maintained with 1.4% isoflurane. In eight animals three levels of PₐCO₂ (25, 40, and 60 mmHg) were studied during 1.4% and 2.8% isoflurane. Mean arterial blood pressure, sagittal sinus pressure, and cerebrospinal fluid pressure were measured and CBF was determined using radiolabeled microspheres. Cerebral perfusion pressure (CPP) was maintained constant at approximately 80 mmHg by inflation of a balloon in the midthoracic aorta. CBF during normocapnia was 70 ± 14 and 118 ± 18 ml·min⁻¹·100 g⁻¹ with 1.4% and 2.8% isoflurane, respectively. As PₐCO₂ was decreased and increased, CBF decreased and increased to 42 ± 7% and 185 ± 16% of control, respectively, during 1.4% isoflurane. During 2.8% isoflurane, hypocapnia decreased CBF to 59 ± 6% of control, but CBF did not increase with hyperventilation. In a second group of animals (n = 9), the effects of changes in CPP during hyperventilation with 1.4% and 2.8% isoflurane were assessed. Increasing CPP approximately 25 mmHg with both 1.4% and 2.8% isoflurane increased CBF but did not change CVR from control. With 1.4% isoflurane, the cerebral vasculature constricts with hypocapnia and dilates with hyperventilation, whereas with 2.8% isoflurane, vasoconstriction to hypocapnia is retained but vasodilation to hyperventilation is absent. Similarity of CBF and cerebrovascular resistance (CVR) during hyperventilation with 1.4% and 2.8% isoflurane in group 1 and the lack of an increase in CVR when CPP was elevated during hyperventilation in group 2 both suggest that hyperventilation produces maximal cerebral vasodilatation. These data suggest that even with isoflurane in concentrations up to 2.8%, hypocapnia can be used to effectively decrease CBF and intracranial pressure. (Key words: Anesthesiology, volatile isoflurane. Brain; cerebral blood flow; cerebral oxygen consumption; cerebral perfusion pressure; cerebrovascular resistance. Carbon dioxide; hypocapnia, hyperventilation.)

CEREBRAL BLOOD FLOW (CBF) increases or decreases as arterial carbon dioxide tension (PₐCO₂) increases or decreases respectively.¹,² This CBF response may be influenced by basal CBF,¹ cerebral O₂ consumption,³ or mean arterial blood pressure (MABP).¹,⁴ Cerebrovascular responsiveness to altered PₐCO₂ occurs in unanesthetized humans⁵ and animals⁶ and in the presence of intravenous anesthetics, such as barbiturates⁷ and synthetic narcotics.⁸

However, responsiveness to changes in CBF during volatile anesthesia is not as clear because basal CBF, cerebral O₂ consumption, and MABP may be altered.

Isoflurane is preferable to other anesthetic gases mainly because of protection during cerebral O₂ deprivation⁹ and decreased brain swelling.¹⁰ Previous studies investigating responsiveness of cerebral vasculature to CO₂ during isoflurane anesthesia have generally emphasized comparison of one concentration of isoflurane with one concentration of other volatile agents.¹⁰,¹¹ Cucchiara et al.¹² found a linear global CBF response to several levels of PₐCO₂ during 1.4% isoflurane but failed to control cerebral perfusion pressure (CPP), to assess more than one isoflurane concentration, or to assess regional responsiveness of cerebral vasculature to CO₂.

Dose related hypotension due to isoflurane makes interpretation of responsiveness of cerebral vasculature to CO₂ difficult because concomitant decreases in CPP alters vessel tone and cerebral vascular resistance. Thus, understanding the effect of isoflurane on responsiveness of cerebral vessels to CO₂ requires dissociation of change in dose from change in MABP.

In the current study, we assessed cerebrovascular responsiveness to alterations in PₐCO₂ during anesthesia with two concentrations of isoflurane (1.4% and 2.8%; 1 and 2 MAC in the dog). We tested the hypothesis that despite dose-related increases in basal CBF with isoflurane, the cerebral vasculature will constrict and dilate as PₐCO₂ is decreased or increased, respectively.

Methods

Mongrel dogs (mixed sex, 20–25 kg) were initially anesthetized with thiopental (12 mg/kg, iv bolus). Following tracheal intubation, their lungs were mechanically ventilated. Anesthesia for surgical preparation consisted of normocapnic ventilation with 1.4% isoflurane (end-tidal) enriched with oxygen (25–30% O₂) to maintain PₐO₂ > 100 mmHg. Isoflurane was administered via a vaporizer designed for isoflurane, and end-tidal isoflurane concentration was monitored using an infrared analyzer (Beckman LB-2®) calibrated with isoflurane calibration gas of 0.5%, 1.0%, and 3.0% (±0.01%) (Scott Medical Products, Plumsteadville, Pennsylvania). End-tidal CO₂ dioxide was monitored using a Beckman LB-2 and maintained at normal levels by adjusting tidal volume or respiratory rate. Catheters were inserted into each omo-

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cervical artery for measurement of MABP and microsphere reference withdrawal. A catheter was inserted retrograde via a femoral artery into the left ventricle for radiolabeled microsphere injection. A balloon tipped catheter (Fogerty®, 10 ml balloon) was placed retrograde via the contralateral femoral artery into the thoracic aorta to allow elevate MABP and CPP during 1.4% and 2.8% isoflurane administration. Balloon inflation with 3–5 ml saline was sufficient to raise MABP to the desired level.

Following placement of the dog in the prone position with the head slightly elevated, pancuronium (5 mg, iv bolus) was administered to decrease muscle contraction due to electrocautery. A catheter was inserted into the sagittal sinus for withdrawal of cerebral venous blood and measurement of sagittal sinus pressure (Pss). A 16-g catheter was inserted into the cisterna magna to measure cerebrospinal fluid pressure (PCSF). Rectal temperature was maintained at 38 ± 1°C by heating lamps. The arterial and sagittal sinus transducers were referenced at the level of the right atrium and the PCSF transducer was referenced to the level of the external auditory meatus. All pressures were measured with Statham P23 dB transducers and recorded on a Gould-Brush Polygraph®. Surgical preparation required approximately 1 h.

**Blood Gas and pH Analysis**

Arterial and cerebral venous blood samples were obtained from the omocervical artery and sagittal sinus, respectively. P\textsubscript{O\textsubscript{2}}, P\textsubscript{CO\textsubscript{2}}, and pH were measured at 37°C immediately after the samples were obtained by use of Radiometer BMS-3® electrodes and analyzer. Oxygen saturation and hemoglobin were measured with an Instrumentation Laboratories CO-oximeter (Model 282®). Arterial and cerebral venous O\textsubscript{2} content were calculated from the measured O\textsubscript{2} saturation and hemoglobin concentration. Cerebral metabolic rate for oxygen (CMRO\textsubscript{2}) was calculated by multiplying hemispheric CBF times the arterial to cerebrovenous O\textsubscript{2} content difference.

**Cerebral Blood Flow Measurement**

CBF was measured with radiolabeled microspheres (15 ± 1.5 μm diameter; Dupont-New England Nuclear Products) using the reference withdrawal method. Six radionizers (\textsuperscript{153}Gd, \textsuperscript{114}In, \textsuperscript{115}Sn, \textsuperscript{103}Ru, \textsuperscript{95}Nb, and \textsuperscript{46}Sc) were injected in random sequence. Prior to each injection, the vial containing the spheres was shaken vigorously and sonicated for 20 min. Approximately 3 × 10\textsuperscript{6} spheres were injected for each measurement of flow. The microspheres were injected into the left ventricle over a 20-s period followed by a 20-s flush of 10 ml of saline. The reference blood sample was withdrawn from the omocervical artery using a Harvard withdrawal syringe pump set at 4.94 ml/min beginning 1 min prior to the injection and continuing for 3 min after the flush. At the end of the experiment, the animal was killed with KCl, and the brain removed and fixed in 10% buffered formalin for 4–7 days.

The brain was cut into the following areas: cerebellum, medulla, caudate, periventricular white matter, and cerebrum (cerebral hemispheres). All tissue samples were weighed and placed in 15-ml poly Q vials and counted in a Packard multichannel autogamma scintillation spectrometer (model 9042) with a 3-inch through-hole NaI crystal. The energy levels of the window settings for the six isotopes were as follows: \textsuperscript{153}Gd, 68–170; \textsuperscript{114}In, 174–230; \textsuperscript{115}Sn, 360–440; \textsuperscript{103}Ru, 450–560; \textsuperscript{95}Nb, 690–820; \textsuperscript{46}Sc, 830–1200 keV. The overlap of activity among isotopes was subtracted to obtain corrected counts for each isotope by solving simultaneous equations using overlap coefficients from pure isotope standards. Blood flow was calculated from the equation, $Q_b = 100 \times (C_b - C_e)/(C_e \times W)$, where $C_b$ is the corrected tissue counts, $Q_b$ is the reference blood sample withdrawal rate in ml/min, $C_b$ is the total corrected counts in the reference arterial blood sample, and $W$ is tissue weight in grams.

**EXPERIMENTAL PROTOCOL: GROUP 1 (N = 8)**

Following completion of surgical preparation, a 30-min period was allowed to adjust ventilation and isoflurane concentration. The respiratory rate was increased to decrease P\textsubscript{ACO\textsubscript{2}} to approximately 25 mmHg and carbon dioxide (CO\textsubscript{2}) added to the ventilator circuit to return P\textsubscript{ACO\textsubscript{2}} to 40 mmHg while continuing hyperventilation. Thus, by altering inspired CO\textsubscript{2} concentration, P\textsubscript{ACO\textsubscript{2}} was altered without changing ventilator rate or tidal volume. In 50% of the animals, the initial isoflurane concentration was 1.4% and in the remaining animals the initial isoflurane concentration was 2.8%. Control data were obtained after 30 min at normocapnia and P\textsubscript{ACO\textsubscript{2}} was then altered by either deleting CO\textsubscript{2} from the inspired gases to lower P\textsubscript{ACO\textsubscript{2}} or increasing inspired CO\textsubscript{2} concentration to elevate P\textsubscript{ACO\textsubscript{2}}. Each level of CO\textsubscript{2} inhalation was maintained for 10 min prior to CBF determination. The alternative change in P\textsubscript{ACO\textsubscript{2}} was then accomplished by altering the inspired CO\textsubscript{2} concentration. Following determination of CBF at normocapnia, hypocapnia, and hypercapnia at the initial isoflurane concentration, normocapnia was reestablished and the alternative isoflurane concentration was achieved and maintained for 30 min. Following determination of CBF during normocapnia at the second isoflurane concentration, P\textsubscript{ACO\textsubscript{2}} was altered in the same sequence as during the initial isoflurane concentration. During ventilation with 2.8% isoflurane, a balloon was inflated in the mid thoracic aorta to increase MABP and produce a CPP similar to that found during 1.4% isoflurane at a similar P\textsubscript{ACO\textsubscript{2}}. In this group, CPP = MABP – Pss. Cerebrovascular resistance (CVR) = CPP/CBF.
Table 1. Hemodynamic and Blood Gas Values in Groups 1 and 2 (mean ± SEM)

<table>
<thead>
<tr>
<th>Group 1 (n = 8)</th>
<th>MABP (mmHg)</th>
<th>PSS (mmHg)</th>
<th>PCSF (mmHg)</th>
<th>CPP (mmHg)</th>
<th>pH</th>
<th>PaO2 (mmHg)</th>
<th>PaCO2 (mmHg)</th>
<th>O2 Content (ml/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoflurane 1.4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hypocapnia</td>
<td>99 ± 2</td>
<td>15 ± 2</td>
<td>7 ± 2</td>
<td>82 ± 4</td>
<td>7.44 ± 0.02*</td>
<td>171 ± 19</td>
<td>25 ± 1*</td>
<td>18.5 ± 1.2</td>
</tr>
<tr>
<td>Normocapnia</td>
<td>100 ± 3</td>
<td>17 ± 1</td>
<td>8 ± 2</td>
<td>82 ± 4</td>
<td>7.31 ± 0.03</td>
<td>167 ± 19</td>
<td>41 ± 2</td>
<td>18.7 ± 1.1</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>98 ± 2</td>
<td>21 ± 2†</td>
<td>12 ± 12†</td>
<td>78 ± 4</td>
<td>7.18 ± 0.02*</td>
<td>175 ± 17</td>
<td>60 ± 3‡</td>
<td>19.6 ± 0.9‡†</td>
</tr>
<tr>
<td>Isoflurane 2.8%</td>
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<tr>
<td>Hypocapnia</td>
<td>98 ± 3</td>
<td>7 ± 2</td>
<td>6 ± 2</td>
<td>81 ± 4</td>
<td>7.44 ± 0.02*</td>
<td>177 ± 21</td>
<td>23 ± 1*</td>
<td>18.2 ± 1.1</td>
</tr>
<tr>
<td>Normocapnia</td>
<td>101 ± 3</td>
<td>21 ± 1</td>
<td>10 ± 2</td>
<td>80 ± 3</td>
<td>7.31 ± 0.02</td>
<td>161 ± 18</td>
<td>41 ± 2</td>
<td>18.6 ± 1.1</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>98 ± 4</td>
<td>21 ± 1</td>
<td>10 ± 2</td>
<td>77 ± 4</td>
<td>7.18 ± 0.02*</td>
<td>184 ± 15</td>
<td>59 ± 3*</td>
<td>18.1 ± 1.0</td>
</tr>
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</table>

Group 2 (n = 8)

| Isoflurane 1.4%     |             |            |             |            |      |             |              |                   |
| Normotension        | 98 ± 3      | 20 ± 3     | 14 ± 3      | 77 ± 3     | 7.20 ± 0.01 | 173 ± 28 | 58 ± 1       | 19.3 ± 0.7       |
| Hypertension I      | 127 ± 6*    | 25 ± 4     | 19 ± 3      | 101 ± 7*   | 7.21 ± 0.01 | 180 ± 28 | 59 ± 2       | 19.1 ± 0.9       |
| Hypertension II     | 153 ± 5*    | 26 ± 3*    | 15 ± 5      | 131 ± 5*   | 7.18 ± 0.02 | 177 ± 30 | 59 ± 3       | 18.1 ± 0.6*†     |

| Isoflurane 2.8%     |             |            |             |            |      |             |              |                   |
| Normotension        | 90 ± 4      | 19 ± 3     | 12 ± 2      | 71 ± 3     | 7.17 ± 0.01 | 169 ± 37 | 61 ± 2       | 19.2 ± 0.9       |
| Hypertension        | 119 ± 7*    | 21 ± 2     | 14 ± 2      | 97 ± 4*    | 7.16 ± 0.01 | 181 ± 29 | 60 ± 2       | 18.0 ± 0.7       |

Values are given as mean ± SEM.

* P < 0.05 compared with normocapnia.
† P < 0.05 compared with hypocapnia.

Experimental Protocol: Group 2 (n = 8)

Following surgical preparation during anesthesia with 1.4% isoflurane, initial isoflurane concentration (1.4% or 2.8%) was maintained along with hypercapnia (PaCO2 approximately 60 mmHg) produced by adding CO2 to the inspiratory circuit. Four animals initially received 1.4% isoflurane and four animals initially received 2.8% isoflurane following surgical preparation. With both isoflurane concentrations, an intracavitary balloon was partially and then fully inflated to elevate CPP to the desired level. CBF was determined at each CPP after a 10-min stabilization period. Following data collection at the initial isoflurane concentration, the intracavitary balloon was deflated, the isoflurane concentration was altered, and the alternative isoflurane concentration (1.4% or 2.8%) was maintained for 50 min. The intracavitary balloon was again inflated and CBF determined. Only a single increase in CPP was possible with 2.8% isoflurane in the presence of hypercapnia because partial balloon inflation was required to elevate control CPP to that found with 1.4% isoflurane. In this group of animals, CPP = MABP - PSS and CVR = CPP/CBF.

Statistical Analysis

Analysis of variance (ANOVA) for repeated measures was performed to assess the effects of isoflurane concentration and PaCO2 in group 1 and isoflurane concentration and CPP in group 2. A P < 0.05 was considered significant and Duncan's multiple range test was used to demonstrate different values. Data in text, table, and figures are presented as mean ± SEM.

Results

Table 1 shows hemodynamic and blood gas values as PaCO2 was altered in group 1 animals (n = 8) and as CPP was altered during constant hypercapnia in group 2 animals (n = 8). In group 1 CPP was similar during 1.4% and 2.8% isoflurane at the three levels of PaCO2. PSS and PCSF changed in similar directions as PaCO2 was altered. pH, PaO2, and arterial O2 content were similar as PaCO2 was changed during 1.4% and 2.8% isoflurane except for a slight increase in arterial O2 content during hypercapnia with 1.4% isoflurane. In group 2 pH, PaO2, PaCO2, and arterial O2 content were unchanged as CPP was altered except for a slight decrease in arterial O2 content with 1.4% isoflurane during the highest CPP.

Figure 1 shows total CBF, CVR, and CMRO2 in group 1 as PaCO2 was changed during ventilation with 1.4% and 2.8% isoflurane. CBF during normocapnia was 70 ± 14 and 118 ± 18 ml·min⁻¹·100 g⁻¹ (P < 0.05) for 1.4% and 2.8% isoflurane, respectively. With 1.4% isoflurane and hypocapnia CBF decreased to 42 ± 7% of control (P < 0.05) and hypercapnia increased CBF to 185 ± 16% of control (P < 0.05). During 2.8% isoflurane and hypocapnia CBF decreased to 39 ± 6% of control (P < 0.05), but CBF was unchanged with hypercapnia. CVR was less during hypcapnia and normocapnia during 2.8% than during 1.4% isoflurane (P < 0.05) but was similar during hypercapnia. CMRO2 during normocapnia was 2.8 ± 0.3 and 2.5 ± 0.4 ml·min⁻¹·100 g⁻¹ for 1.4% and 2.8% isoflurane, respectively, and was unchanged with hypcapnia or hypercapnia at either isoflurane concentration.

Figure 2 shows regional CBF in group 1 as PaCO2 was altered during 1.4% and 2.8% isoflurane. With 1.4% isoflurane, flow in all regions increased and decreased as
Figure 4 shows total CBF, CVR, and CMRO₂ in group 2 as CPP was increased during 1.4% and 2.8% isoflurane and hypercapnia (Paco₂ approximately 60 mmHg). With 1.4% isoflurane, increasing CPP from 77 ± 3 to 101 ± 6 mmHg increased CBF by 23%, whereas during 2.8% isoflurane, increasing CPP from 71 ± 3 to 97 ± 7 mmHg increased CBF by 39% (P < 0.05). CVR remained approximately 0.5 mmHg · ml⁻¹ · min⁻¹ · 100 g⁻¹ with both 1.4% and 2.8% isoflurane as CPP was increased during hypercapnia. Control CMRO₂ was 2.7 ± 0.4 ml · min⁻¹ · 100 g⁻¹ for 1.4% and 2.8% isoflurane and was unchanged as CPP was altered.

Figure 5 shows regional CBF in group 2 animals as CPP was elevated. Control blood flow during 1.4% and 2.8% isoflurane was similar in all regions. Elevation of CPP from 77 ± 3 to 101 ± 6 mmHg during 1.4% isoflurane did not increase blood flow in cerebrum or medulla but did increase flow in caudate, white matter, and cer-

PaCO₂ increased and decreased. With 2.8% isoflurane, regional blood flow in all areas decreased as PaCO₂ decreased from 41 to 23 mmHg (P < 0.05) but did not increase in any area as PaCO₂ was elevated to 59 mmHg.

Figure 3 shows regional responsiveness of cerebral vasculature to CO₂ (final CBF - initial CBF)/(final PaCO₂ - initial PaCO₂) in group 1 animals. Within each region, cerebral vascular responsiveness to CO₂ was similar with hypocapnia during 1.4% isoflurane, hypercapnia during 1.4% isoflurane, and hypocapnia during 2.8% isoflurane. However, responsiveness to CO₂ in all regions was less (P < 0.05) except in white matter with hypercapnia during 2.8% isoflurane.
ebellum ($P < 0.05$). An additional increase of CPP to 131 ± 5 mmHg increased ($P < 0.05$) blood flow in cerebrum (142%), caudate (192%), white matter (183%), medulla (143%), and cerebellum (149%). With 2.8% isoflurane, elevation of CPP from 71 ± 5 to 97 ± 7 mmHg increased CBF ($P < 0.05$) in cerebrum to 139% of control, caudate to 147% control, white matter to 149% of control, medulla to 132% of control, and cerebellum to 138% of control.

**Discussion**

We found that cerebrovascular responsiveness to $P_{CO_2}$ is retained during both 1.4% and 2.8% isoflurane anesthesia. During 1.4% isoflurane, CBF decreased as $P_{CO_2}$ decreased and increased as $P_{CO_2}$ increased and the response was similar in magnitude to that previously found during barbiturate and narcotic anesthesia. However, we found a somewhat different response to altered $CO_2$ during 2.8% isoflurane. Cerebrovascular responsiveness to decreased $P_{CO_2}$ (from normocapnia to hypocapnia) during 2.8% isoflurane was similar to that found during 1.4% isoflurane. However, cerebrovascular responsiveness to increased $P_{CO_2}$ (from normocapnia to hypercapnia) was diminished. With 2.8% isoflurane, CBF failed to increase with hypercapnia in brain regions with high basal blood flow (caudate) and brain regions with low basal blood flow (white matter). In group 1 constant CPP excluded hemodynamic changes as the cause of failure of CBF to increase with $P_{CO_2}$ elevation. Our results are in general agreement with those of Cucchiara et al. in that the response to changes in CBF with $P_{CO_2}$ are linear with 1.4% isoflurane. However, we found a larger response in the change from hypocapnia to hypercapnia (from 44% to 186% of normocapnia control) compared with the results of Cucchiara et al. who at similar $P_{CO_2}$ found CBF of 55% and 130% of normocapnia control, respectively.
In that study, CPP was not reported; consequently, it is unclear if CPP was maintained constant during \( P_{\text{aCO}_2} \) alteration.

Our data show similar CBF and CVR with hypocapnia (\( P_{\text{aCO}_2} = 60 \text{ mmHg} \)) during 1.4% and 2.8% isoflurane and suggest that hypocapnia causes maximal cerebral vasodilation with both 1.4% and 2.8% isoflurane (fig. 1). Group 2 animals were studied to determine whether the CBF found with 1.4% and 2.8% isoflurane during hypocapnia represents maximal CBF in this model. We found that during isoflurane with hypocapnia, flow in all regions increased with 2.8% isoflurane as CPP was increased by approximately 25 mmHg, which is consistent with previously demonstrated failure of autoregulation at that isoflurane concentration. With 1.4% isoflurane and hypocapnia regional flow increased in caudate, white matter, and cerebellum but not cerebrum and medulla during a similar increase in CPP suggesting partial retention of autoregulation, also consistent with a previous study. The effect of hypocapnia on cerebral autoregulation is controversial even in studies using similar anesthesia in the same species. For instance, Haggendal and Johansson found preserved autoregulation during hypocapnia (\( P_{\text{aCO}_2} = 60 \text{ mmHg} \)), whereas in the same species and with the same anesthesia, Harper and Ekstrom-Jodal et al. found that hypocapnia abolished autoregulation.

The failure of hypocapnia to increase CBF during 2.8% isoflurane raised the question of maximal vasodilation. In the intact animal, there are two basic approaches to assessing the degree of vasodilation. First, a known potent vasodilator can be administered while other factors such as CPP are controlled. Second, the response of CVR can be observed as interventions that alter CBF are performed. We chose the latter for several reasons. The only nonpharmacologic intervention available to cause vasodilation is hypoxia, which has not been extensively studied in the presence of isoflurane. Additionally, the hemodynamic depression of hypoxia combined with hypocapnia would almost certainly prevent adequate control of CPP. Therefore, we elected to observe CVR while CPP was elevated. We reasoned that because 2.8% isoflurane (normocapnia) produces a pressure passive cerebral vasculature, if 2.8% isoflurane somehow prevents vasodilation with hypocapnia, that effect might be overcome by an increase in CPP. The failure of CVR to decrease supports maximal vasodilation.

Two potential criticisms of our study are the use of thiopental (12 mg/kg, iv bolus) to induce anesthesia initially and the time required for data collection over which changes in CBF might occur. It is unlikely that the thiopental affected interpretation of our results for two reasons: 1) the order of isoflurane concentration and \( P_{\text{aCO}_2} \) was varied and 2) the dose of barbiturate was sufficiently small that drug effects on CBF should not have persisted into the study period. Additionally, we found similar total and regional CBF during isoflurane to that found by Boarini et al. who did not use a barbiturate to induce anesthesia.

Previous studies assessing maximum regional CBF using the microsphere method have found values similar to those of the present study at similar CPP. However, Warner et al. found a higher CBF in the dog (250 ml·min\(^{-1}\)·100 g\(^{-1}\)) at MAP of 122 mmHg. With elevation of CPP to 131 mmHg in group 2 (1.4% isoflurane), total CBF was similar to that reported by Warner et al. suggesting that a higher CPP is the cause of higher CBF in that study.

With 2.8% isoflurane, cerebrovascular responsiveness as \( P_{\text{aCO}_2} \) decreased from normocapnia to hypocapnia was...
approximately 3.4 ± 0.6 ml·min⁻¹·100 g⁻¹·mmHg⁻¹ (white matter, 1.5 ± 0.4 ml·min⁻¹·100 g⁻¹·mmHg⁻¹), but responsiveness as PaCO₂ increased from normocapnia to hypercapnia was less in all regions except white matter. Cerebrovascular responsiveness to CO₂ appears dependent on experimental design, anesthetic level, and species. Cerebrovascular responsiveness to CO₂ of 1.4–2.8 ml·min⁻¹·100 g⁻¹·mmHg⁻¹ have been reported in anesthetized animals and 6.3 ml·min⁻¹·100 g⁻¹·mmHg⁻¹ in unanesthetized animals with both homogenous regional cerebrovascular responsiveness and heterogenous regional cerebrovascular responsiveness.

The higher cerebrovascular responsiveness to CO₂ of cerebrum, cerebellum, and caudate compared with white matter is similar to that previously reported. Rosenberg et al. found in awake animals that responsiveness in brain stem, cerebellum, cerebrum, and caudate are similar at approximately 6.3 ml·min⁻¹·100 g⁻¹·mmHg⁻¹, whereas white matter responsiveness is much less (1.6 ml·min⁻¹·100 g⁻¹·mmHg⁻¹). With 1.4% isoflurane, we found a cerebrovascular responsiveness to CO₂ of 2.6–3.2 ml·min⁻¹·100 g⁻¹·mmHg⁻¹ (white matter 1.4 ± 0.4 ml·min⁻¹·100 g⁻¹·mmHg⁻¹). Increased responsiveness during 2.8% isoflurane may be explained by the observation of Ackerman et al. who found that basal MABP and hence vessel tone affects responsiveness. They found that the higher the vascular conductance, the greater the cerebrovascular responsiveness to CO₂. Thus, the lower CVR, the greater would be the change in CBF with changes in PaCO₂. Our findings of greater responsiveness to CO₂ with 2.8% isoflurane is consistent with their findings.

The basal CMRO₂ has been reported to affect CO₂ responsiveness, with a linear relationship between change in CBF and change in PaCO₂ and CMRO₂ in human (r = 0.58) and anesthetized dogs (r = 0.77). Because CMRO₂ was similar with 1.4% and 2.8% isoflurane, the difference in responsiveness to CO₂ found in the present study cannot be by this mechanism.

We found a relatively small difference in CMRO₂ between 1.4% and 2.8% isoflurane compared with that previously reported. Several important methodologic considerations may explain the apparent difference. In the models used in those studies, 1) CBF is responsive to systemic vasopressors; 2) the higher dose of isoflurane was administered sequentially so that any degradation of the preparation with time would emphasize the difference between low (1.4%) and high (2.8–3.0%) concentrations of isoflurane; 3) increased concentration of isoflurane decreased MABP (ICP not reported); and 4) higher concentration of isoflurane required higher doses of phenylephrine to support MABP. The importance of administering isoflurane doses in the same order (low then high) is suggested by the work of Turner et al. who studied the effect of time on CBF during constant 0.8% isoflurane (plus 70% N₂O to equal 1.3 MAC). In that study, CMRO₂ was decreased by as much as 29% following several hours of isoflurane administration at a constant concentration. Additionally, Boarini et al. found an approximate 20% decrease in CMRO₂ over time with 1.5% isoflurane. However, Albrecht et al. found that with halothane CMRO₂ was decreased and then returned toward normal with time.

Potential errors due to study design may contribute to inaccuracies in computing CMRO₂ because 1) CBF is increased dramatically with the combination of isoflurane and hypercapnia; 2) coincidentally, cerebral venous oxygen content is increased as a result of the increased CBF so that the arterial to cerebral venous oxygen content difference used to compute CMRO₂ is low; and 3) the order of isoflurane concentration and other interventions were randomly applied. Thus, our study design should effectively negate the effect of time on the interpretation of our results, but randomization of dose may have contributed to increased experimental error in the circumstance of relatively high measurement error due to the low arterial to cerebral venous O₂ content difference.

In the present study, we excluded drug-produced hypotension by nonpharmacologically reversing isoflurane-induced hypotension. Although this experimental manipulation clarifies interpretation of the effects of changes on PaCO₂ changes during normotension and hypotension, these data do not give insight into cerebrovascular responsiveness to CO₂ during hypotension. However, our data are compatible with those from previous investigators concerning induced hypotension by volatile anesthetic agents. Artru found that responsiveness to CO₂ is partially preserved during isoflurane hypotension to 50 mmHg (PaCO₂ decreased from 40 to 20 mmHg, CBF decreased by 25%). Our data would suggest that even with the maximum dose of isoflurane used in that study (2.6% isoflurane), responsiveness to CO₂ is in competition with autoregulatory vasodilation. In our previous study, an MABP of 50 mmHg would produce a CPP of approximately 45 mmHg, which produces a nadir of CVR with 2.8% isoflurane, which is the same CVR as that found with 1.4% isoflurane. Thus, the partial preservation of responsiveness to CO₂ may simply be a function of CPP above the lower limit of autoregulation.

In conclusion, cerebrovascular responsiveness to CO₂ is retained during both 1 and 2 MAC isoflurane (1.4% and 2.8%) in the dog. However, with 2.8% isoflurane, hypercapnia fails to increase CBF due to existing maximal vasodilation. Our data suggest that the ability to alter CBF with changes in PaCO₂ depends on the isoflurane concentration. With both 1.4% and 2.8% isoflurane, hypocapnia decreases CBF compared to normocapnia. Although CBF...
is decreased with 2.8% isoflurane and hypocapnia, CBF is still higher than at the same \( \text{PaCO}_2 \) with 1.4% isoflurane.

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