Anesthesiology
73:461-466, 1990

The Influence of Halothane, Isoflurane, and Pentobarbital on Cerebral Plasma Volume in Hypocapnic and Normocapnic Rats

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Cerebral blood volume (CBV = cerebral plasma volume [CPV] + cerebral red cell volume [CRBCV]) is one determinant of intracranial pressure. In an effort to quantitate the effects of anesthetics and Pa_{CO_2} on CBV, the authors measured cerebral plasma volume (CPV) in normocapnic ($Pa_{CO_2} \approx 42$ mmHg) and hypocapnic ($Pa_{CO_2} \approx 22$ mmHg) rats receiving 1 MAC doses of isoflurane or halothane, or given an approximately equivalent dose of pentobarbital. All animals were paralyzed, their lungs mechanically ventilated, and body temperature kept normal throughout the study. CPV was measured using ^{14}C-labeled dextran, a large (70,000 molecular weight [M.W.]), nondiffusible compound that was given intravenously and allowed to circulate for ≈5 min. The experiments then were terminated by freezing the brains *in situ* with liquid N_2 poured into a funnel affixed to the exposed calvarium. Isotope concentrations in solubilized brain and in plasma were determined by scintillation counting, and CPV was calculated as the ratio between these values. CPV during both hypocapnic and normocapnic pentobarbital anesthesia was less than with either volatile agent. During normocapnia, CPV for pentobarbital = 2.1 ± 0.26 ml/100 g (mean ± SD, n = 8), compared with 2.96 ± 0.44 ml/100 g (n = 9) and 3.06 ± 0.44 ml/100 g (n = 9) for halothane and isoflurane, respectively. There were no differences in CPV between the two volatile agents during normocapnia. However, during hypocapnia, CPV in isoflurane-anesthetized animals decreased to 2.29 ± 0.43 ml/100 g, as compared with 2.68 ± 0.36 ml/100 g with halothane ($P < 0.05$) and 1.86 ± 0.33 ml/100 g for pentobarbital (not significant *vs.* isoflurane, $P < 0.01$ for pentobarbital *vs.* halothane). The magnitude of these differences—particularly the changes produced by Pa_{CO_2}—appears to be smaller than previously published differences in cerebral blood flow (CBF), which supports suggestions that it may be invalid to equate changes in CBF with changes in brain blood volume or intracranial pressure. (Key words: Anesthetics, intravenous: barbiturates; pentobarbital. Anesthetics, volatile: halothane; isoflurane. Brain: cerebral blood volume; cerebral blood flow; intracranial pressure. Neuroanesthesia.)

BOTH VOLATILE AND INTRAVENOUS ANESTHETICS can influence intracranial pressure (ICP). Because the ICP change produced by anesthetics usually begins within a very short time after the onset of drug administration, it is unlikely that it initially reflects changes in either tissue water or cerebrospinal fluid (CSF) volume. These early changes are probably due to changes in cerebral blood volume (CBV).[1-3] However, there has been relatively little quantitative work done concerning the CBV effects of anesthetic drugs. In two papers published in 1983 and 1984, Artru[1,2] examined the effects of halothane, enflurane, isoflurane, and fentanyl on CBV in dogs, measured as *changes* in plasma volume relative to an N_2O-anesthetized control state, using ^{131}I-labeled serum albumin (RISA). He noted that the three volatile agents produced 8–11% increases in volume (no significant differences between agents, although all increased CPV relative to the preanesthetic state), whereas fentanyl resulted in a decrease. In 1983, Drummond *et al.*[3] measured the effects of the same volatile agents on the protrusion of the brain through a craniectomy, an approach that provides an indirect assessment of changes in at least some component of brain volume, presumably CBV. In contrast to the work of Artru, these results suggested that halothane resulted in substantially larger increases in brain volume (and perhaps CBV) than either enflurane or isoflurane. However, none of these studies directly quantitated CBV (in ml/100 g of brain). More recently, Archer *et al.*[4] quantitated the effects of changing isoflurane concentrations, N_2O, and Pa_{CO_2} on CBV in dogs, using positron emission tomography (PET) and ^{11}CO-labeled red blood cells. They observed that isoflurane increased CBV by 31% in normocapnic animals, and by 15% during hypocapnia (relative to a control anesthetic state achieved with thiopental and fentanyl). Finally, Artru compared CBV in dogs with an intracranial mass lesion anesthetized with halothane, enflurane, isoflurane, thiopental, or fentanyl.[5] In contrast to his earlier studies in dogs with normal intracranial pressures,[1,2] he found no differences in CBV, and essentially identical decreases when Pa_{CO_2} was decreased from 37 to 21 mmHg (about 20%).

In an effort to better understand the effects of anesthetics, we have employed ^{14}C-labeled dextran as a plasma marker to directly measure cerebral *plasma* volume (CPV), where CBV = CPV + cerebral red cell volume. Using this tracer, we determined the relative CPV effects of 1-MAC concentrations of halothane and isoflurane under both normocapnic and hypocapnic conditions, and compared these values with those obtained during an approximately equivalent depth of pentobarbital anesthesia.

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Received from Neuroanesthesia Research Group, Department of Anesthesia, University of Iowa College of Medicine, Iowa City, Iowa. Accepted for publication March 30, 1990. Supported in part by NIH grants RO1-NS24517 (Dr. Todd) and R29-GM39771 (Dr. Warner). Dr. Warner is also a recipient of the Parker B. Francis Award. Presented in part at the XIVth International Cerebral Blood Flow Meeting, Bologna, Italy, May 1989, and at the 1989 Annual Meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 1989.

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Methods

All experiments were approved by the University of Iowa Animal Use Committee.

Fifty-four male Sprague-Dawley rats weighing 400 ± 25 g (mean ± SD) were placed in a plastic box, and according to a predetermined random sequence were anesthetized with 4–5% halothane or isoflurane in O_2. After infiltration of the incision site with 1% lidocaine, a tracheostomy was performed with a 14-G cannula, and the animals' lungs ventilated with a tidal volume of 3.5 ml at a rate of ≈55 breaths/min, using an inspired gas mixture containing ≈1–1.5 MAC concentrations of halothane or isoflurane in 40% O_2/balance nitrogen. Rectal temperature was maintained at 37–38° C throughout the experiment, using a servo-controlled warming pad. Catheters (PE-50) were then surgically inserted via into both femoral arteries and one femoral vein (again after 1% lidocaine infiltration). Succinylcholine (≈1.6 mg) was given intravenously (iv) and the animal turned prone. The head was fixed into a stereotaxic frame, with the interaural line ≈1 cm above the midchest. After infiltration with lidocaine, a midline scalp incision was made, and the skin edges and periosteum were reflected. After hemostasis was achieved, the 27-mm diameter spout of a large funnel (supported by a ring stand) was secured over the exposed skull using a purse-string suture. 100 units of heparin then was given iv.

In all animals surgical preparations were completed within 50 min.

Halothane and Isoflurane Groups

On completion of the surgical preparation, the inspired concentration of either halothane or isoflurane was adjusted to 1 MAC in 36 rats (halothane = 1.0%, n = 18; isoflurane = 1.5%, n = 18, as monitored by a Datex Model 222 Anesthetic Agent Analyzer™). The ventilator then was adjusted to deliver a tidal volume of 4.5 ml at a rate of 75 breaths/min. Animals were then further assigned to one of two subgroups (n = 9 each). In hypocapnic animals, Pa_{CO_2} was allowed to decrease to target values of ≈22 mmHg, while in normocapnic rats, CO_2 was added to the inspired gas mixture to insure a Pa_{CO_2} of ≈40 mmHg.

Pentobarbital Group

Animals assigned to the pentobarbital group (n = 18) were anesthetized with either halothane or isoflurane (in equal numbers) and prepared in a fashion identical to that described above. On completion of the surgical period, the volatile anesthetics were discontinued, and 50 mg/kg of pentobarbital was given iv over ≈8 min. This dose was chosen on the basis of preliminary studies that demonstrated that ≈50% of animals would move in response to a tail clamp 1 h after drug administration (*i.e.*, at the time of volume determination). In addition, animals were assigned to hypocapnic and normocapnic groups as noted above (n = 9 each).

After surgical preparation and group assignments were completed, anesthesia was maintained using the selected anesthetic/Pa_{CO_2} conditions for 55 min. Arterial blood gas concentrations/*p*H were measured at 15, 30, and 45–50 min after group assignment. In addition, a 0.3-ml sample of blood was drawn at 45 min after group assignment for the determination of Hct, and for use as a "blank" for subsequent radioactivity determinations. Mean arterial pressure as recorded from one of the femoral arterial catheters was maintained between 90 and 110 mmHg in all animals, either by the infusion of homologous donor blood or by blood withdrawal. A collective total of 2.4 mg of succinylcholine was injected in divided doses at 0, 15, and 40 min after group assignment.

Approximately 50 min after group assignment, the final arterial blood sample was drawn and 16 μCi of ^{14}C-Dextran (70,000 molecular weight [M.W.], American Radiolabeled Chemicals, St Louis, MO) was given as an iv bolus in a volume of ≈0.4 ml of saline. Five minutes later, a 0.2-ml sample of arterial blood was drawn, and liquid N_2 was poured into the funnel affixed to the animal's skull. Thirty seconds after the initial liquid N_2 application, an additional 0.2 ml of arterial blood was drawn. The two arterial samples were mixed to ensure that the reference blood sample adequately "bracketed" the period of brain freezing. The funnel was kept full of liquid N_2 for another 5 min, during which time the heart was stopped with saturated KCl (at 3 minutes after initially pouring liquid N_2 into the funnel). The funnel then was removed, and the calvarium dissected away from the brain, along with the dura and dural vessels. With the brain still frozen, a coronal cut was made through the olfactory portion of the frontal poles, and through the cerebrum just anterior to the confluence of venous sinuses. A final midsagittal cut separated the brain into left and right hemispheres, which were removed from the skull and placed on a prefrozen aluminum plate. Each hemisphere then was transferred to separate preweighed scintillation vials, weighed, dried at 55° C for 3 days, and weighed again.

Sample Processing

Fifty-microliter samples of blood were solubilized with 1 ml of NCS (Amersham, Arlington Heights, Ill) at 55° C for 20 min. The samples were cooled, decolorized with 200 μl of benzoyl peroxide (0.2 g/ml of toluene), and neutralized with 15 μl of glacial acetic acid. Each sample then was suspended in 18 ml of scintillation cocktail (3a70, Research Products International, Mt. Pleasant, IL). The

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TABLE 1. Arterial Blood Gases, Hemodynamic Variables, and Brain Weights

	Halothane		Isoflurane		Pentobarbital		
	Hypo	Normo	Hypo	Normo	Hypo	Normo	Significance
N	9	9	7	9	9	8	
Pa_{O_2} (mmHg)	152 ± 36	169 ± 30	136 ± 34	149 ± 24	172 ± 23	182 ± 23	NS
Pa_{CO_2} (mmHg)	22 ± 1	41 ± 2	24 ± 1	41 ± 2	23 ± 1	41 ± 3	As intended
*p*H	7.63 ± 0.02	7.43 ± 0.02	7.60 ± 0.02	7.42 ± 0.04	7.61 ± 0.04	7.42 ± 0.04	As intended
Hct (%)	42 ± 2	42 ± 2	42 ± 2	43 ± 2	41 ± 3	41 ± 1	NS
MAP (mmHg)	99 ± 5	102 ± 6	104 ± 5	101 ± 6	103 ± 4	105 ± 3	NS
Blood in (ml)	2.8 ± 1.3	2.1 ± 1.7	0.7 ± 1.0	2.4 ± 1.3	−5.3 ± 1.4	−4.2 ± 1.9	*
Brain, wet weight (g)	1.302 ± 0.049	1.317 ± 0.078	1.286 ± 0.069	1.310 ± 0.064	1.309 ± 0.088	1.314 ± 0.059	NS
% Water content	78.06 ± 0.44	78.32 ± 0.34	78.40 ± 0.28	78.17 ± 0.42	78.42 ± 0.32	78.58 ± 0.20	NS

Pa_{O_2}, Pa_{CO_2}, pH, Hct, and MAP values obtained just before *in situ* brain freezing (mean ± SD).

Values for wet weight and percent water represent data obtained from combining both left and right hemispheric samples.

* $P < 0.05$ for both pentobarbital groups *versus* all others.

dried cerebral hemispheres were rehydrated with 500 μl of water, and then dissolved overnight in 4 ml of NCS (55° C). After cooling, the solution was neutralized with 136 μl glacial acetic acid, and then suspended in 17 ml scintillation cocktail.

All samples were placed in a dark cabinet for 5 days to reduce chemoluminescence. They then were counted on a Tracor Analytic Mark III™ scintillation counter. Counts per minute (CPM) for both blood and brain were converted to decays per minute (DPM) using calibration curves constructed with ^{14}C-labeled benzoic acid standards (New England Nuclear, Boston, Mass). Radioactivity in blood was expressed as DPM/μl, whereas that in brain was expressed as DPM/mg wet weight.

CALCULATIONS

^{14}C-Dextran is a plasma marker. If measured arterial Hct and tissue Hct were identical, this tracer could be directly used to measure CBV. However, brain tissue Hct is lower than large vessel Hct.[6–10] Furthermore, the ratio between brain and large vessel Hct may vary with differing physiologic conditions.[10] Our results are therefore most accurately expressed as cerebral *plasma* volume (CPV), rather than as CBV (which is the sum of plasma and red cell volumes). Cerebral plasma volume was calculated according to the following equation[7,§]:

$$\text{CPV (ml/100 g)} = \frac{\text{brain radioactivity (DPM/mg wet weight)} \times 100}{\text{blood radioactivity (DPM/}\mu\text{l)}} \times (1 - \text{arterial Hct})$$

STATISTICS

All statistical analyses were performed using a two-way factorial analysis of variance (ANOVA), with anesthetic and Pa_{CO_2} (hypocapnic or normocapnic) as between-group factors. When indicated, post-hoc pairwise comparisons were carried out using a Student-Newman-Keuls test. A *P* value of <0.05 was considered significant.

Results

Nine animals were initially entered into each of the six groups. Errors in sample processing resulted in loss of data from three animals (two hypocapnic isoflurane, one normocapnic pentobarbital). There were no intergroup differences in Pa_{O_2}, Hct, or MAP (table 1). The Pa_{CO_2} and *p*H varied as intended. Animals receiving halothane or isoflurane required the infusion of blood to maintain blood pressure (BP) at the desired level, while most rats given pentobarbital required phlebotomy (table 1).

Cerebral plasma volume data are shown in figure 1, and intergroup statistical comparisons are shown in figure 2. During both normocapnia and hypocapnia, CPV was lower with pentobarbital than with either of the volatile agents. In addition, CPV during hypocapnia was lower during isoflurane anesthesia than with halothane, in spite of the similar CPV values seen for the two agents during normocapnia. However, the differences between hypocapnic and normocapnic CPVs in halothane and pentobarbital groups did not achieve statistical significance.

§ We were initially concerned that changes in CBV would be associated with changes in measured tissue wet weight. If this were true, then wet weights would vary from group to group in parallel with CBV, *i.e.*, an increase in the amount of blood per hemisphere would lead to an increased number of counts and to an increase in weight. This might lead to an underestimate of actual CBV. However, examination of both our hemispheric wet weights and the per cent water calculations for the groups showed no differences (See Table 1).

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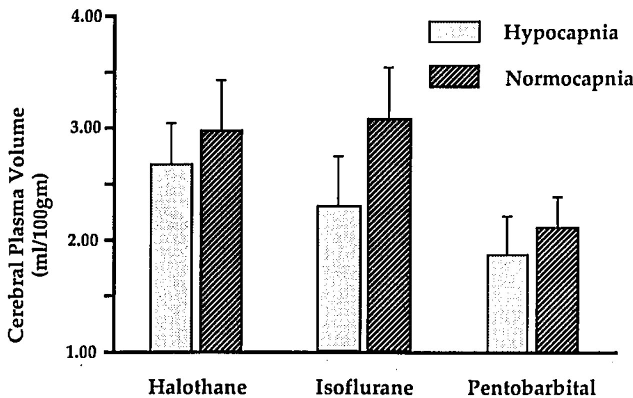

FIG. 1. Cerebral plasma volume values (mean ± SD, ml/100 g wet weight) in the six experimental groups, divided according to hypo- or normocapnia. For statistical comparisons, see figure 2.

The differences in measured CPV were not reflected by any differences in either brain wet weight or water content (table 1).

Discussion

Cerebral blood volume plays an important role in determining the ICP response to anesthetic agents, but in spite of many studies examining the cerebral blood *flow* changes produced by anesthetics, relatively little information is available concerning CBV.[1-5] If CBF and CBV changed in parallel, this lack of data would be of little consequence. However, there are numerous experimental examples showing that CBF and CBV do *not* change in parallel.[11,12,13-15] Grubb *et al.*[11] noted that the slope of the CBV-*versus*-Pa_{CO_2} response curve in monkeys was much flatter than that for CBF *versus* Pa_{CO_2}; reducing Pa_{CO_2} from 40 to 20 mmHg reduced CBF from ≈55 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ to 19 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ (a 65% decrease), whereas CBV decreased from 3.6 ml/100 g to 2.8 ml/100 g (a 22% decrease). A similar observation was noted by Risberg *et al.*[12] In fact, these relatively "flat" CBV/Pa_{CO_2} curves are similar to the small responses seen to CO_2 in our rats, and in dogs as studied by Artru.[5] In 1976, Gado *et al.*[16] measured a 37% increase in CBV during pentylenetetrazol (Metrazol)-induced seizures (4.1 to 5.6 ml/100 g), whereas CBF increased by 390% (from 38 to 187 $ml \cdot 100\ g^{-1} \cdot min^{-1}$). In addition, measurements made during ischemia have shown an increase in CBV occurring at a time when CBF is low,[13,14] while Michenfelder and Milde[15] recently demonstrated that the administration of nitroprusside was capable of increasing ICP (an indirect measure of changing CBV) with no accompanying change in CBF. With respect to the influence of anesthetics, Theye and Michenfelder[17] noted in 1968 that 1 MAC halothane (added to a background of 70% N_2O) increased CBF from 60 to 85 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ (a 42% increase). However, Artru[1] reported that a similar concentration of halothane (also added to N_2O) increased CBV (actually CPV) by only 11%.

These inequalities between changes in CBF and CBV are not difficult to understand, particularly when one recognizes that the bulk of intracranial blood is located in postarteriolar vessels (*e.g.*, veins).[18] Although there is no reason to believe that these vessels should be insensitive to the vasoactive properties of anesthetics, there is also no reason to believe that they will respond in a fashion identical to regions that control flow (*i.e.*, arterioles). We hence believe that it is unwise to assume that a measured change in CBF will represent a similar change in CBV. Perhaps more importantly it would also seem to be inappropriate to conclude that an observed change in CBF will result in some predictable change in ICP, or that one drug will produce a greater increase in ICP than another, simply because it produces a greater effect on CBF. Such conclusions require direct measurements of either ICP or CBV.

There are several methodologic issues concerning the current study that need to be discussed. First, we measured only the plasma component of CBV. As mentioned in "Materials and Methods," double-label studies (*e.g.*, ^{51}Cr-labeled red cells and ^{131}I-labeled albumin) demonstrate that cerebral tissue Hct is lower than that in large vessels, with a tissue/large vessel Hct ratio of 0.7–0.85 being variously reported for small animals.[6-9] If this ratio were constant under all conditions, it would be possible to correct our CPV values and calculate total CBV. However, Sakai *et al.*[10] have suggested that the tissue/large vessel Hct ratio may change under various conditions. This suggests that it may be misleading to convert measured CPV values to total CBV. Nevertheless, there is no reason to believe that our measurements of CPV do not reflect general intergroup differences in CBV.

The second issue concerns the method by which the brains were frozen and the animals killed. In two recent

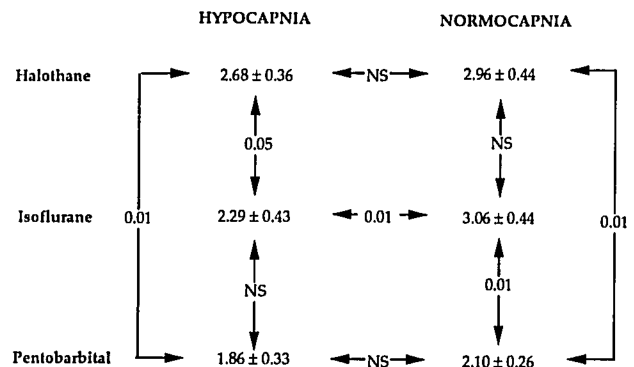

FIG. 2. Measured CPV values and statistical comparisons. Values are means ± SD, expressed as ml/100 g of brain tissue. Statistical analysis using two-way ANOVA with post-hoc Newman-Keuls testing.

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rat studies on CBV[7,19] animals were killed by decapitation or drug overdose, and the brains removed while still warm. The potential for losing blood from the intracranial space is obvious, and our CPV values are larger than the values obtained by such decapitation methods. For example, Cremer *et al.*,[7] studying animals killed by decapitation or pentobarbital overdose, obtained CPV values in various brain regions of 0.44–1.00 ml/100 g, whereas Todd *et al.*[19] measured a dextran distribution space of 1.6 ml/100 g in halothane-anesthetized animals killed by decapitation.[7,19] By contrast, Everett *et al.*[6] froze pentobarbital-anesthetized rats in liquid N_2 and obtained a CPV = 2.12 ml/100 g (*vs.* 2.10 ml/100 g in our animals).[6] These findings suggest that *in situ* freezing is preferable to decapitation. However, it may still not be ideal. Using a surface funnel method,[20] full-depth freezing requires 30–45 s, leaving the possibility that CBV in areas more distant from the dorsal surface of the brain may change before the freezing front reaches them. However, Archer *et al.*[4] measured CBV by PET scanning in living animals, using carbon monoxide-labeled red cells. Estimated CPV in that study during 2.0% isoflurane was ≈3.2 ml/100 g (our calculation). This compares with a value of 3.01 ml/100 g in our normocapnic isoflurane-anesthetized animals, suggesting that our observed values are reasonable. Nevertheless, we recognize that the ideal sacrifice method would be one that instantaneously fixes blood in place, or at least one that prevents any blood from leaving the intracranial space during the freeze. Possibilities include focused microwave radiation, or the use of a very high-pressure neck tourniquet applied at the same time as the liquid N_2. We are exploring both possibilities for future studies.

The final issue to be addressed concerns the apparent relationship between CPV and the volume of blood infused or withdrawn from animals in the various groups (which was done to control blood pressure). There is no question that these volume alterations seem to change in parallel with the measured CPV values. It hence might be argued that our CPV measurements are not due to anesthetic effects on the brain, but are somehow related to changes in whole body blood volume. We believe this to be unlikely, for several reasons. First, the infusion or withdrawal of blood presumably alters BP via its effects on cardiac output—a circulatory parameter that has little influence on cerebral blood flow and hence, presumably, little effect on cerebral blood volume (although this has not been directly studied). It is possible that blood infusion/withdrawal might alter right atrial pressures (RAP) differently in the different anesthetic groups, with resultant differences in cerebral venous pressures (which would alter CPV). However, in a separate study carried out to examine this possibility, we measured RAP in normocarbic halothane- and pentobarbital-anesthetized animals in which blood volume was altered in the fashion used for this study (*i.e.*, to achieve mean arterial pressure of 100 mmHg). Under such conditions, right atrial pressure differed by only 1 mmHg between groups, a difference we believe is unlikely to influence CPV significantly. In addition, linear regression analysis of CPV *versus* blood in/out within individual groups (*i.e.*, within the normocarbic halothane group) show no significant correlations. As a result of these considerations, we feel that it is far more likely that the relationship between CPV and blood in/out is coincidental; drugs like halothane and isoflurane dilate *both* the cerebral and peripheral vasculature, whereas in this species pentobarbital appears to constrict both. In addition, we believe that this approach to the experiment is preferable to either 1) permitting widely different BP values between groups, or 2) controlling BP using vasoactive drugs.

Given these caveats, we believe that our results reflect the differences in CBV that exist between the various anesthetic/Pa_{CO_2} conditions that were studied. As expected, CPV during pentobarbital anesthesia was significantly lower than that observed with either of the volatile agents. Of greater interest were the essentially identical CPV values noted during normocapnia with both halothane and isoflurane, but the presence of a steeper CPV–Pa_{CO_2} response curve for isoflurane. The similar values seen during normocapnia would seem to conflict with the belief that halothane is a more potent vasodilator than is isoflurane.[21,22] However, recent work by Hansen *et al.*[23] has suggested that halothane and isoflurane produce markedly different patterns of flow distribution within the brain, and that these earlier reported "differences" may be due to the measurement methods used. In addition, this same work indicated that "whole brain" CBF at 1 MAC was identical for the two agents. More importantly, two publications by Madsen *et al.*,[24,25] who measured global CBF in humans with the Kety-Schmidt technique (hence avoiding any problems with regional specificity), noted very similar CBF values during equi-MAC doses of halothane and isoflurane. These CBF findings combined with our CPV measurements suggest that these two drugs may have very similar acute ICP effects during normocapnia, although we also realize that ICP changes over longer periods may be influenced by factors other than CBV, including changes in CSF volume and dynamics.[1,2,5,26] Although the ICP effects of halothane and isoflurane have never been directly compared in humans, Scheller *et al.*[27] saw nearly identical ICP increases with the two agents in normocapnic brain-injured rabbits. This may not be true during hypocapnia, and our observations of a steeper CPV/Pa_{CO_2} responsiveness for isoflurane appears to correspond qualitatively with the CBF–Pa_{CO_2} response curves obtained for these agents by Drummond and Todd,[28] in which CBF at a Pa_{CO_2} ≈20 mmHg was

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lower during isoflurane anesthesia than with halothane. Similar results were obtained by Scheller *et al.*[29] However, Scheller *et al.* also noted that the ICP responses to halothane and isoflurane were similar during hypocapnia,[27] and hence we must be careful about trying to extrapolate CBV and CBF data to more "clinically relevant" circumstances, and it may be that our results are not applicable to situations in which the brain is injured, or in which ICP is elevated.[5] Furthermore, our measurements were made 1–2 h after the initial administration of the agents, and we cannot rule out the possibility that transient differences in volume were present (see ref. 3).

In summary, we have compared the effects of three anesthetics and Pa_{CO_2} on CBV by the use of a radioactive plasma marker and measurements of CPV. Our results indicate that barbiturate anesthesia, during both normocapnic and hypocapnic conditions, results in consistently lower cerebral plasma volumes than do either of the volatile agents studied. In addition, CPV values were essentially identical during normocapnic isoflurane and halothane anesthesia. Finally, although the slopes of the CPV–Pa_{CO_2} response curves for all three agents appear to be much "flatter" than published CBF–Pa_{CO_2} curves, the slope of the response curve seen during isoflurane anesthesia is significantly steeper than with halothane.

The authors would like to thank John Tinker, M.D., for his continued encouragement and support.

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