

## Distribution of Cerebral Blood Flow During Halothane Versus Isoflurane Anesthesia In Rats

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The effects of halothane *versus* isoflurane on distribution of cerebral blood flow (CBF) were compared using  $^{14}\text{C}$ -iodoantipyrine autoradiography. Sprague-Dawley rats were exposed to 1 MAC of either halothane ( $n = 8$ ) or isoflurane ( $n = 7$ ) in 33%  $\text{O}_2$ /balance nitrogen for 55 min prior to determination of CBF. Normoxia, normothermia, and normocapnia were maintained throughout the experiment and mean arterial pressures (MAP) were held within the range of 90–100 mmHg by infusion of blood. Coronal autoradiographic brain images were then digitized and optical density values converted to CBF with the use of  $^{14}\text{C}$  autoradiographic standards and arterial radioactivity data. Hemispheric, neocortical, subcortical, and selected local anatomical regions were defined on a cathode ray screen display by cursor outline. Mean CBF for each region was determined at each of eight standardized coronal brain sections, and area weighted average values for the whole brain were also calculated. Hemispheric CBF was identical in the two anesthetic groups: halothane =  $150 \pm 16 \text{ ml} \cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1}$ ; isoflurane =  $147 \pm 19 \text{ ml} \cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1}$ . However, neocortical CBF was greater in halothane anesthetized animals (halothane =  $185 \pm 16 \text{ ml} \cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1}$ ; isoflurane =  $154 \pm 19 \text{ ml} \cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1}$ ,  $P = .004$ ). The authors conclude that halothane and isoflurane exert regionally selective effects on CBF with halothane appearing to have a more pronounced effect on the neocortex. Previously reported discrepancies concerning the relative effects of these two agents on CBF may be due to inherent differences in the tissue regions measured by the different techniques. (Key words: Anesthetics, volatile; halothane; isoflurane. Brain: cerebral blood flow. Measurement technique: autoradiography.)

VOLATILE ANESTHETICS have long been known to alter cerebral blood flow (CBF) in many species, including humans.<sup>1,2</sup> While numerous studies have examined the effects of halothane and isoflurane anesthesia on CBF,<sup>3-8</sup> some controversy still remains with respect to the relative influences of these two agents. For example, Cucchiara *et al.*<sup>5</sup> and Stullken *et al.*<sup>6</sup> showed only small differences in CBF when comparing halothane *versus* isoflurane anesthesia in dogs. By contrast, others have measured larger CBF values during halothane anesthe-

sia.<sup>3,7,9</sup> However, these results relied upon different CBF determination methods, each with its own inherent anatomical sampling bias. For example, the venous outflow method employed by Cucchiara *et al.*<sup>5</sup> and Stullken *et al.*<sup>6</sup> measures flow in both cortical and subcortical structures in the forebrain.<sup>10</sup> By contrast, Scheller *et al.* examined only cortical flow using the hydrogen clearance technique,<sup>7</sup> while the  $^{133}\text{Xe}$  washout technique employed by Todd *et al.* measures predominantly cortical CBF, and the method used by Eintrei *et al.* looks at the most superficial layers of the cortex.<sup>9</sup>

Given this information, we postulated that halothane and isoflurane may lead to differences in the relative distribution of CBF within the brain. In other words, CBF determination methods that differ in anatomical sampling sites, *e.g.*, the venous outflow method *versus*  $^{133}\text{Xe}$  washout, may yield different results during identical anesthetic conditions. To examine this hypothesis, we evaluated the effects of 1 MAC halothane and isoflurane anesthesia on hemispheric, neocortical, and subcortical CBF in the rat using the  $^{14}\text{C}$  iodoantipyrine autoradiographic method.<sup>11,12</sup> This method offered the advantage of simultaneously measuring CBF in multiple brain regions. Thus, misinterpretation of CBF results due to anatomical sampling bias could be minimized.

### Materials and Methods

The study was approved by the institutional Animal Care and Use Committee. Male Sprague-Dawley rats weighing between 310 and 390 g (Biolabs; St. Paul, MN) received rat chow and water until the time of the study. Animals were randomly assigned to either halothane or isoflurane experimental groups and accordingly were anesthetized with 1.5% halothane or 2.0% isoflurane in 33%  $\text{O}_2$ /balance nitrogen. A tracheostomy tube was inserted and connected to a small animal ventilator set to deliver a tidal volume of 2.5 ml at a rate of 60/min. Femoral arterial and venous catheters were inserted *via* cutdown, and all wound sites were infiltrated with 2.0% lidocaine. The arterial catheter was connected to a pressure transducer for continuous blood pressure monitoring while the venous catheter was used for drug and fluid administration. Heparin

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(200 IU) and d-tubocurarine (2 mg) were administered intravenously to each rat.

Total surgical preparation time was 35 min (measured from the start of induction). Following surgery, inspired anesthetic agent concentration (measured with a Puritan Bennett/Datex Model 222 Anesthetic Agent Analyzer) was reduced to either 1 MAC isoflurane (1.38%) or 1 MAC halothane (1.05%) in 33% O<sub>2</sub>/balance nitrogen.<sup>13</sup> Rats were then ventilated an additional 55 min. Pilot studies indicated that, at this point in time, end-tidal anesthetic agent concentrations closely approximated inspired values for both agents (halothane end-tidal = 95% inspired values, isoflurane end-tidal = 96% inspired values). Blood gases were measured throughout the experiment at 15-min intervals using an automated blood gas analyzer (Radiometer ABL-2, Copenhagen, Denmark) with values reported in table 1 obtained immediately prior to injection of isotope. The ventilator was adjusted to maintain normoxia (PaO<sub>2</sub> = 110–140 mmHg), and normocarbica (PaCO<sub>2</sub> = 38–42 mmHg). Blood volume from arterial blood gas sampling was replaced with donor rat whole blood. Body temperature was monitored *via* a rectal probe and maintained within the range of 36.5–37.5° C by surface heating or cooling. Mean arterial pressure (MAP) was continuously monitored and maintained within the range of 90–100 mmHg by infusion of donor rat whole blood.

#### CBF DETERMINATION

Following a 55-min exposure period to 1 MAC concentrations of the selected inhalational agent, animals

TABLE 1. Physiological Values

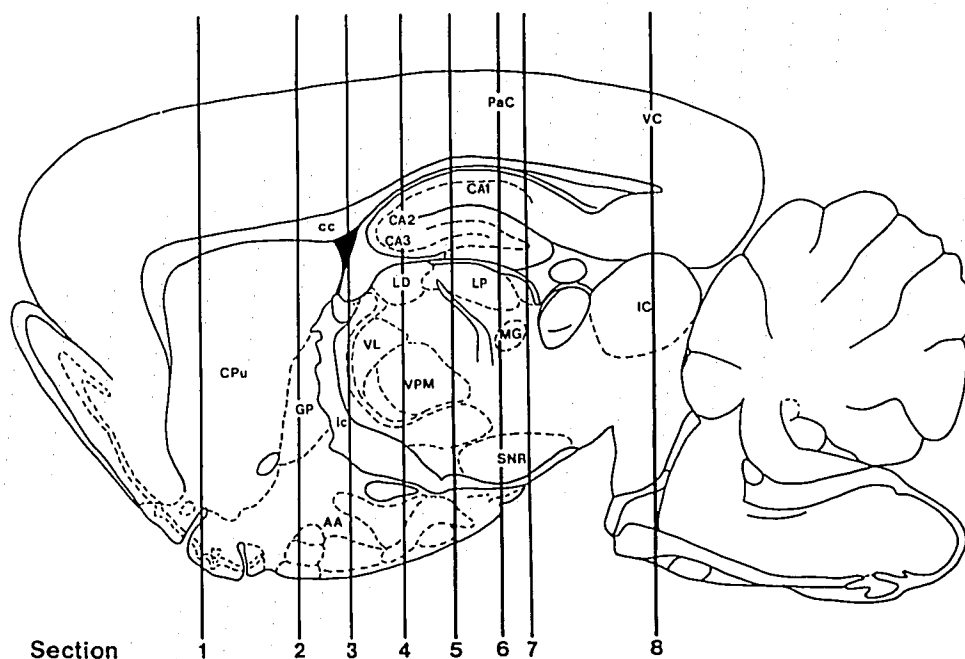
	Halothane (n = 8)	Isoflurane (n = 7)
MAP (mmHg)	95 ± 4.0	96 ± 4.0
PaCO <sub>2</sub> (mmHg)	39.5 ± 2.0	39.0 ± 1.7
PaO <sub>2</sub> (mmHg)	134 ± 32	110 ± 21
pHa	7.38 ± .04	7.37 ± .04
Rectal temp (°C)	36.9 ± .2	37.0 ± .2

Physiological values (mean ± SD) controlled during the administration of 1 MAC halothane and isoflurane. Values were recorded immediately prior to CBF determination. There were no significant differences.

were given an additional 2 ml donor rat whole blood. Final MAP and arterial blood gas values were recorded and 75 µCi/kg of <sup>14</sup>C-labeled iodoantipyrine (<sup>14</sup>C-IAP, specific activity 60 mCi/mmol, New England Nuclear, Boston, Massachusetts) was infused intravenously at a constant rate over 45 s *via* an infusion pump. During this time, ten discontinuous 20 µl arterial blood samples were collected for later determination of arterial <sup>14</sup>C activity. Upon completion of the isotope infusion, animals were decapitated, and the brains were rapidly removed and frozen in 2-methyl butane (–40° C). If brain removal required more than 2 min (following decapitation), animals were discarded.

Arterial blood samples were placed on chromatography paper, dried for 24 h, and then eluted an additional 24 h in a mixture of 1 ml water and 9 ml liquid scintillation cocktail (Ready-Solv™ HP/b, Beckman, Fullerton, CA). Radioactivity was then determined by liquid

FIG. 1. Anatomical location of autoradiographic brain images selected for CBF analysis. Saggital section is 2.9 mm lateral to the midline. LD = lateral dorsal thalamic nucleus; LP = lateral posterior thalamic nucleus; VL = ventro-lateral thalamic nucleus; VPM = ventro-posterior medial thalamic nucleus; CA1, CA2, CA3 = hippocampal subfields; AA = anterior amygdala; CPu = caudo-putamen; SNR = substantia nigra; PaC = parietal cortex; VC = visual cortex, IC = inferior colliculus, GP = globus pallidus. Modified from Paxinos G, Watson C: The Rat Brain: A Stereotactic Atlas. New York, Academic Press, 1982, with permission.



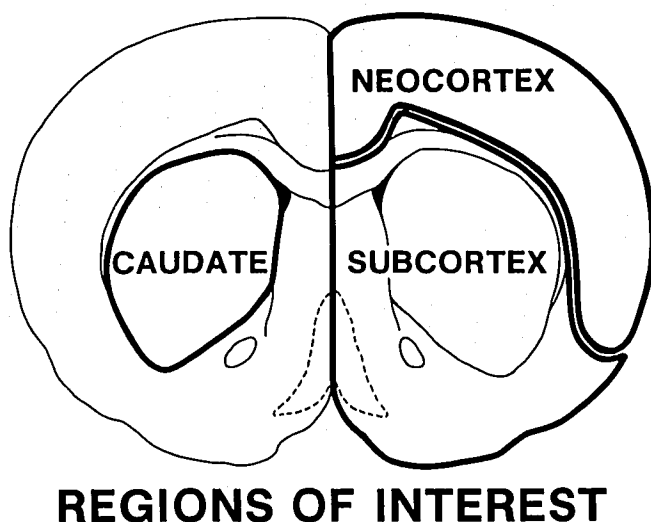


FIG. 2. Cursor outlines of selected anatomical regions in a coronal brain section. Brain section corresponds to section level 1 (fig. 1).

scintillation counting (Model 6880, Searle, Des Plaines, Illinois) using an external quench correction.

#### AUTORADIOGRAPHY AND IMAGE ANALYSIS

Brains from eight halothane- and seven isoflurane-anesthetized animals were analyzed. Frozen brains were cut in 20  $\mu\text{m}$  thick serial coronal sections on a cryostat at  $-20^\circ\text{C}$ . Quadruplicate sections taken at 240- $\mu\text{m}$  intervals were mounted on glass slides, dried for 5 min on a  $50^\circ\text{C}$  hot plate, and exposed to Kodak SB-5 autoradiographic film for 7 days in an x-ray cassette along with seven  $^{14}\text{C}$ -methylmethacrylate standards (Amersham, Arlington Hts, Illinois). Images of eight brain sections from each animal were chosen for further analysis, based upon standardized anatomical landmarks (fig. 1). These autoradiographic images were converted to digitized optical density images on a scanning microdensitometer system (Eikonix-Kodak, Bedford, Massachusetts) using a camera aperture of 100  $\mu\text{m}$ . Tissue optical densities were converted to  $^{14}\text{C}$  concentration by comparison with pre-calibrated standards and this information, along with arterial blood radioactivity data, was entered into equations developed by Reivich *et al.*<sup>11</sup> and modified by Sakurada *et al.*<sup>12</sup> Mathematical operations were performed using the National Institutes of Health cerebral blood flow program (C Patlak, Bethesda, MD).

#### DATA ANALYSIS

Individual digitized CBF images were pseudo-color enhanced and displayed on a cathode ray screen. Using an operator-controlled cursor, regions of interest were circumscribed and average CBF for that region was re-

corded, along with the area of that region (in pixel units). The three primary regions of interest in each section were hemisphere, neocortex, and subcortex, where subcortex was defined as the hemispheric area minus the area of the cortical mantle. The margins of these regions are shown in figure 2. Olfactory cortex is a limbic structure and was, therefore, included in subcortex,<sup>14</sup> and ventricular spaces were subtracted from the images prior to CBF calculations. A two-way ANOVA (section level *versus* anesthetic agent with section level as a repeated variable) was then used to compare the values for each region.

In addition to these larger regions, CBF was also determined for caudate, thalamus, hippocampus, amygdala, lateral septal nucleus, median preoptic area, hypothalamus, and the inferior colliculus. These values were compared between anesthetic groups using the Student's unpaired *t* test.

To provide an estimate of "global" values for the various regions, hemispheric neocortical, and subcortical CBF values from each section were area weighted and averaged over the eight sections within each rat. Area weighted pooled values were then compared between anesthetic groups by an unpaired Student's *t* test.

Physiological values were compared between anesthetic groups by unpaired *t* testing. One animal from each inhalational group was dropped from the study due to  $\text{PaCO}_2$  values deviating greater than two standard deviations from mean  $\text{PaCO}_2$  values for their respective experimental group; one animal was excluded from the isoflurane experimental group due to brain removal time exceeding 2 min. Values throughout are reported as mean  $\pm$  standard deviation with statistical significance assumed when  $P < .05$ .

#### Results

Physiologic values immediately prior to CBF determination are reported in table 1. No significant differences were noted between anesthetic groups with respect to MAP,  $\text{PaO}_2$ ,  $\text{PaCO}_2$ , pH, or body temperature. Infused blood volumes were  $3.8 \pm .3$  ml and  $3.7 \pm .2$  ml for the halothane and isoflurane groups, respectively.

Hemispheric CBF was nearly identical in the two inhalational groups at each of eight brain levels analyzed (fig. 3A), and subcortical flows were also similar. However, *neocortical* CBF in the halothane group was higher than with isoflurane in six of eight brain levels analyzed (fig. 3B), the largest difference being noted in section level 3 (halothane =  $189 \pm 22$  ml  $\cdot$  100 gm<sup>-1</sup>  $\cdot$  min<sup>-1</sup>; isoflurane =  $145 \pm 27$  ml  $\cdot$  100 gm<sup>-1</sup>  $\cdot$  min<sup>-1</sup>,  $P < 0.004$ ). These differences are schematically depicted in figure 4.

Table 2 summarizes "whole brain" CBF results for

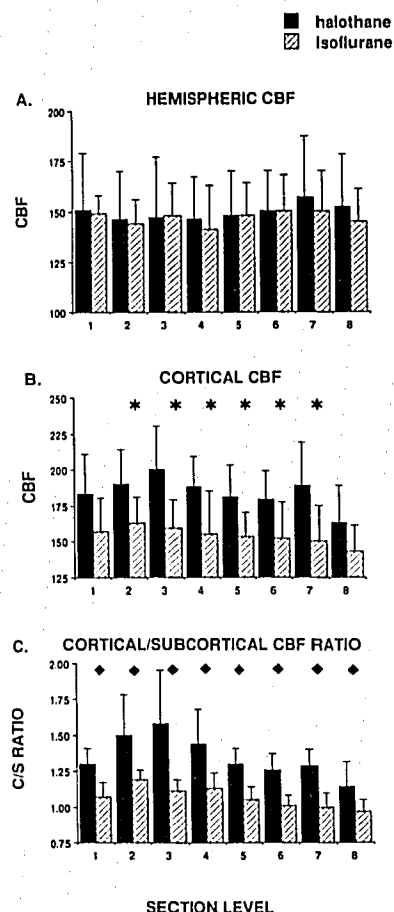
the three major tissue regions (calculated as an area weighted average of the eight sections). Mean hemispheric CBF was identical in the two inhalational groups ( $P = .63$ ), as was subcortical CBF. By contrast, neocortical CBF, as well as the neocortical/subcortical CBF ratio, was greater in the halothane group. There were no significant anesthetic-related differences in the CBF values determined for the eight selected (subcortical) structures, although  $0.05 \leq P < 0.1$  for the amygdala, lateral septal nucleus, and median preoptic area.

### Discussion

Our results indicate that while "whole-brain" and hemispheric CBF are similar during both halothane and isoflurane anesthesia, the distribution of flow within the brain is different for each agent. In particular, neocortical blood flow is much greater during 1 MAC halothane than during an equipotent concentration of isoflurane.

These observations must, of course, be treated cautiously. Area weighted CBF values pooled from eight standardized brain sections were taken to reflect whole brain values. However, the brain sections chosen for analysis were based on the subcortical anatomical structures within these sections, not the uniformity of antero-posterior distance between brain sections. Examination of the anatomical location of our selected sections shows a relative bias toward centrally located sections at the expense of more rostral and caudal regions (fig. 1). Inclusion of a greater number of brain sections within these latter regions may have altered interpretation of our results. In addition, it must also be realized that the area (volume?) of the neocortical and subcortical regions were different, with subcortical regions being  $\approx 2.1$  times larger than the neocortex. This size difference explains the observation that while cortical flows were different between anesthetics, hemispheric and "whole-brain" flows (which are dominated by the subcortical contribution) were not. However, these neocortical and subcortical area differences will also differ from species to species, and, hence, extrapolation of our results must be tempered. For example, if

FIG. 3. A. Hemispheric CBF values. B. Cortical CBF values. C. Cortical/subcortical CBF ratio values calculated from sections 1 through 8 during 1 MAC halothane and 1 MAC isoflurane anesthesia. \* =  $P < .05$ ;  $\diamond = P < .01$ .



the neocortex were to occupy a larger fraction of the total brain area, we might expect to see greater "whole-brain" CBF values with halothane than with isoflurane.

We believe our results may help explain certain conflicts that exist within the literature on halothane and isoflurane. For example, in some of the earliest work with halothane and isoflurane, Stullken *et al.*<sup>6</sup> and Cucchiara *et al.*<sup>5</sup> found only very small differences in the CBF effects of these two agents in dogs, using the venous outflow method. In a more recent experiment in our laboratory, Kaieda *et al.* also noted nearly identical halothane and isoflurane CBF values in the rabbit,

FIG. 4. Schematic representation of coronal autoradiographic CBF images during 1 MAC halothane and isoflurane anesthesia. Brain section corresponds to section levels 1 and 4 (fig. 1) CBF in  $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ . Ctx = cortex; CPu = caudo-putamen; Hip = hippocampus; Thl = thalamus; Amg = amygdala.

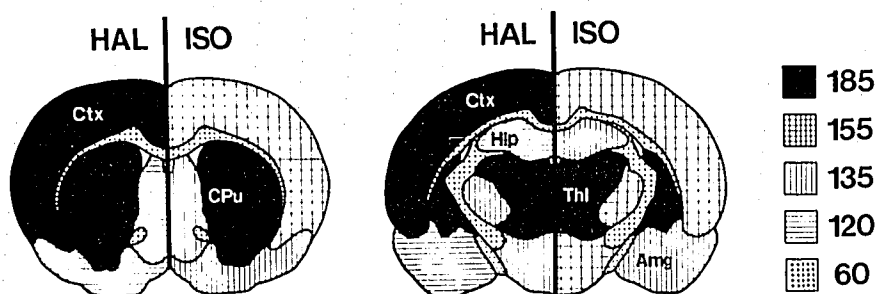


TABLE 2. Cerebral Blood Flow Values

Region	Halothane (n = 8)	Isoflurane (n = 7)	P Value
Hemisphere	150 ± 16	147 ± 19	NS
Subcortex	139 ± 17	144 ± 12	NS
Neocortex	185 ± 16	154 ± 19	.004
Caudate nucleus	185 ± 16	176 ± 29	NS
Thalamus	162 ± 16	176 ± 30	NS
Amygdala	121 ± 16	138 ± 14	.05
Hippocampus	132 ± 17	143 ± 11	NS
Hypothalamus	125 ± 26	136 ± 14	NS
Inferior colliculus	184 ± 41	188 ± 24	NS
Lateral septal nucleus	118 ± 15	134 ± 19	.07
Median preoptic area	122 ± 20	140 ± 15	.09

Cerebral blood flow values ( $\text{ml} \cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1}$ , mean  $\pm$  SD) of selected regions during 1 MAC halothane and isoflurane anesthesia. *P* values determined from unpaired *t* testing. Values above the dashed line are derived from area weighted values pooled over all eight anatomical sections.

using a platinum  $\text{H}_2$  flow electrode placed in the confluence of cerebral venous sinuses.<sup>15</sup> However, both of these methods measure predominantly "whole-brain" (or, more accurately, forebrain) flows. By contrast, Todd and Drummond<sup>3</sup> and Eintrei *et al.*<sup>9</sup> both used variations of the  $^{133}\text{Xe}$  washout technique to measure CBF, a method that primarily "sees" cortical regions. In fact, the method used by Eintrei *et al.* involved the direct application of Xe to the cortical surface. Both of these studies revealed significantly greater flows during halothane than during isoflurane anesthesia. In addition, both Scheller *et al.*<sup>7</sup> and Kaieda *et al.*,<sup>15</sup> using cortically implanted  $\text{H}_2$  electrodes, demonstrated greater CBF values with halothane.

While our results are in general agreement with previous studies,<sup>3,5-9</sup> there are differences between those studies and our current work that should be recognized. The most notable being species differences; our study has examined the CBF effects of anesthetics in the rat, while others have studied the cat,<sup>3</sup> dog,<sup>5,6,8</sup> rabbit,<sup>7</sup> and human.<sup>9</sup> In addition, we have examined the effects of halothane and isoflurane on CBF in the absence of additional anesthetics. Studies performed by Cucchiara *et al.*,<sup>5</sup> Todd *et al.*,<sup>3</sup> Scheller *et al.*,<sup>7</sup> and Eintrei *et al.*<sup>9</sup> involved other drugs, most notably nitrous oxide. It is possible that, when halothane or isoflurane are added to a background of nitrous oxide, the result may be different than when either agent is used alone.<sup>16</sup> However, the degree to which nitrous oxide influenced the results of these studies is unknown.

Other studies have examined the effects of halothane and isoflurane on CBF using autoradiography.<sup>4\*\*</sup> However, direct correlation with our own study is not possible because these studies sampled multiple small

regions rather than large areas. Nevertheless, Ray *et al.* reported CBF values from parietal cortex (sensorimotor) and hippocampus of  $191 \text{ ml} \cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1}$  and  $103 \text{ ml} \cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1}$ , respectively, during 1 MAC halothane anesthesia,\*\* while Maekawa *et al.* observed CBF values of  $147 \text{ ml} \cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1}$  and  $130 \text{ ml} \cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1}$ , respectively, in these same areas during 1 MAC isoflurane anesthesia.<sup>4</sup> The ratio of neocortical to hippocampal CBF values shows values of 1.85 for halothane, versus 1.11 for isoflurane. Similarly, the authors have noted that the ratio of neocortical to subcortical CBF at each section level was consistently greater during halothane compared to isoflurane anesthesia, suggesting that the distribution of CBF in the neocortex relative to subcortical structures is different between anesthetic agents. (fig. 3).

The cause of differences in distribution of flow with these two agents is unclear. It is possible that halothane is a more potent direct cerebral vasodilator than isoflurane. However, in that case, higher subcortical flows would also have been observed, with similar neocortical/subcortical ratios for the two drugs. Isoflurane is a more potent metabolic depressant than halothane.<sup>3,5,6,8</sup> If flow and metabolism remain coupled, then it is possible that these differences may also be reflected in differences in flow—assuming that isoflurane is having a disproportionate effect on the neocortex. However, until we are able to examine local CMR using autoradiographic methods, this remains entirely speculative.

Recognition of the differences in the regional distribution of CBF during halothane and isoflurane anesthesia may be of value in understanding anesthetic effects in experimental pathological states, as well as in evaluating the anesthetic effects upon intracranial pressure (ICP). For example, increases in CBF may be associated with parallel increase in cerebral blood volume and ICP.<sup>17</sup> However, Todd and Drummond, using the xenon clearance technique, noted an apparent contradiction; despite greater increases in CBF during halothane anesthesia, increases in ICP were identical for both halothane and isoflurane. Since the xenon clearance method measures predominantly cortical CBF, it is possible that the observed differences in CBF were not representative of whole-brain differences. In fact, the comparable increases in ICP would support the idea that both agents had similar effects on whole-brain cerebral blood volume (and CBF)—a finding confirmed by the work of Artru.<sup>18,19</sup> In addition, understanding the differences in the distribution of CBF during halothane and isoflurane anesthesia may have applications in ex-

\*\* Ray KF, Kohlenberger RW, Shapiro HM: Local cerebral blood flow and metabolism during halothane and enflurane (abstract). ANESTHESIOLOGY 51: S10, 1979.

perimental pathological states, such as stroke models, in which the regional effects of anesthetic agents may alter the location of a focal infarction.<sup>20</sup>

In summary, despite identical hemispheric and subcortical flows, halothane is associated with higher cortical CBF than isoflurane. We suggest that understanding the differences in sampling sites inherent in various CBF determination techniques is critical in interpreting the comparative effects of anesthetics. The cause of the selective effects of halothane and isoflurane on CBF is unknown, but may be related to their different metabolic effects,<sup>21</sup> or perhaps to differential vasodilating capabilities of the anesthetic agents.††

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