

## Relationship between Cerebral Blood Volume and CSF Pressure during Anesthesia with Halothane or Enflurane in Dogs

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Cerebral blood volume (CBV) and intracranial pressure (ICP) were examined in dogs during 3.5 h anesthesia with halothane (0.8%) or enflurane (2.2%), and after decreasing the concentration of halothane to <0.1% or enflurane to <0.2%. As compared with animals breathing N<sub>2</sub>O and O<sub>2</sub>, halothane (0.8%) increased CBV 11-12%, while ICP remained increased (4-5 cmH<sub>2</sub>O) for 3.5 h. Both at 0.8% and <0.1% ICP correlated positively with changes in CBV. Enflurane (2.2%) increased CBV by 8-10%, and while ICP correlated with changes in CBV during the initial 30 min, ICP increased independently of CBV thereafter. (Key words: Anesthetics, volatile; enflurane; halothane. Brain: blood flow; blood volume; intracranial pressure.)

INTRACRANIAL PRESSURE (ICP) CHANGES produced by anesthetics commonly are attributed to anesthetic-induced changes in cerebral blood flow (CBF). The effects of commonly used anesthetics on CBF are well-known as a result of numerous animal studies that permit reliable comparisons between anesthetics.<sup>1-7</sup> However, ICP is determined not by CBF *per se*, but rather by the volume of the cerebral vascular compartment.<sup>8</sup> There have been no comparative studies of the effects of commonly used anesthetics on cerebral blood volume (CBV). Thus, it is not known whether changes in ICP are directly related to CBV with these anesthetics. One purpose of this study was to examine CBV and ICP during anesthesia with halothane or enflurane in dogs.

Another determinant of ICP is the volume of the cerebrospinal fluid (CSF) space. Recent evidence suggests that increased CSF volume may contribute in part to increased ICP during anesthesia with halothane or enflurane. In short-term (8-min infusions) manometric studies in rats, Mann *et al.* reported that both halothane (1 MAC) and enflurane (1 MAC) caused an increase in the rate of CSF production ( $\dot{V}_f$ ).<sup>9,10</sup> Enflurane (1 MAC) also caused increased resistance to reabsorption of CSF. In long-term (5.0-5.5 h) ventriculocisternal perfusion studies in dogs, Artru and Michenfelder subsequently reported that the increase in  $\dot{V}_f$  caused by 2.2% enflurane was of sufficient magnitude and duration that

an increase in ICP should result due to increased CSF volume.<sup>11</sup> A second purpose of the present study was to examine for increases in ICP which were not associated with increased CBV and which therefore may be attributed to increased CSF volume during anesthesia with halothane or enflurane in dogs.

### Methods

Eighteen unmedicated mongrel dogs (weights, 12-19 kg) were studied. Anesthesia was induced with either enflurane (>2.5%, six dogs) or halothane (>1.0%, 12 dogs) in nitrous oxide (N<sub>2</sub>O, 60-70%) and oxygen. The trachea was intubated and ventilation was controlled with a Harvard® pump and adjusted along with the inspired oxygen concentration to maintain initial blood gases (Radiometer BMS3 Mk2® electrodes) at PaO<sub>2</sub> > 120 mmHg and PaCO<sub>2</sub> = 34 ± 1 mmHg (mean ± SEM). With the animal in the lateral position, a urinary catheter was placed and the right femoral vein was cannulated for fluid and drug administration. Intravenous infusion of 50-115 mg/h succinylcholine maintained muscle relaxation. The right femoral artery was cannulated for arterial blood sampling for blood-gas analysis and continuous monitoring of systemic arterial pressure and heart rate. Mean arterial pressure (MAP) was determined by electronic integration. Expired CO<sub>2</sub> was monitored continuously using a Beckman LB-2® medical gas analyzer. Temperature was monitored by esophageal thermister probe and maintained at 37 ± 0.5° C by heat lamps or ice packs. Depletion of vascular volume was minimized by continuous infusion of 4-6 ml · kg<sup>-1</sup> · h<sup>-1</sup> saline.

Relative cerebral blood volume (CBV) was determined by measuring gamma emission from intravenously injected iodinated <sup>131</sup>I albumin (RISA).<sup>†12,13</sup> With the animal in the prone position and the head slightly elevated and fixed in a stereotaxic frame, a midline scalp incision was made and the muscles reflected laterally. Over the right parietal region the skull was thinned around the perimeter of a 4 × 5 cm area to expose diploic veins that were then occluded with bone wax. A converging (5-inch focal length) collimated

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scintillation probe (NaI) was placed over the exposed region at right angles to the head and 45° from horizontal. The "window" of the detector (Picker Nuclear Magnascanner 500®) was set at 250 to 450 KeV and the time constant was set at 20 s. Sufficient RISA was injected to provide counting rates of 1,000 to 2,000 cpm. Following intravenous injection of RISA, 80 min were allowed for equilibration prior to determining CBV. Total gamma emission detected by the probe derives primarily from intracerebral blood with some contribution from both background activity and extracranial blood in tissues on the opposite side of the head from the probe. Total gamma emission was measured during the study and the values later used to calculate relative CBV by correcting for the contribution from both background activity and extracranial blood.<sup>13</sup>

CSF pressure was measured via cannulae placed into a lateral cerebral ventricle and into the cisterna magna. An open-ended 18-gauge Teflon® cannula fitted with a blunt tip stylet was directed through a left parietal burr hole into the underlying lateral ventricle. The burr hole was sealed and the catheter was affixed to the skull using methyl methacrylate resin.‡ An open-ended, fine-tipped, tapered glass cannula was directed into the cisterna magna following dissection of the posterior neck muscles. A short length of fine nylon tubing connected each cannula to a strain gauge transducer (Statham®, P 23 AA) referenced to zero at the level of the external auditory meatus. Ventricular and cisternal CSF pressures were recorded as mean pressures via electronic integration. ICP was defined as mean intraventricular CSF pressure. In all dogs CBV, ICP, and systemic variables were determined 20–25 min after the CSF cannulae were placed and RISA had equilibrated.

Dogs then were divided into three groups of six dogs each for determination of CBV, ICP, and systemic variables. In one group (six dogs surgically prepared under halothane anesthesia), the inspired concentration of halothane was decreased and the dogs maintained on N<sub>2</sub>O (60–70%) and halothane (<0.1%) in O<sub>2</sub> (controls). Halothane anesthesia was chosen for surgical preparation of controls because, unlike enflurane, prolonged anesthesia with halothane does not increase  $\dot{V}_f$  in dogs, and when the concentration of halothane is decreased to <0.1%,  $\dot{V}_f$  returns to control values in <45 min (author's unpublished studies). In this control group, CBV, ICP, and systemic variables were determined for 5 h after decreasing the concentration of halothane to <0.1%. The remaining two groups (six dogs surgically prepared under halothane anesthesia, and six dogs surgically prepared under enflurane anesthesia) were examined at the following conditions in sequence: preex-

posure period (45–50 min), prolonged anesthesia (3.5 h), and postexposure period (45–50 min). Anesthetic concentrations for the pre- and postexposure periods were N<sub>2</sub>O (60–70%) and either halothane (<0.1%) or enflurane (<0.2%) in O<sub>2</sub>. Prolonged anesthesia was maintained with either halothane (0.8%) or enflurane (2.2%) and N<sub>2</sub>O (60–70%) in O<sub>2</sub>. Concentrations of halothane and enflurane were end-expired values determined by gas chromatography. In all three groups, cerebral and systemic values were determined at 5-min intervals when conditions were being changed, and at 10- to 30-min intervals when conditions were steady. PaCO<sub>2</sub> was maintained at PaCO<sub>2</sub> = 34 ± 1 mmHg in all animals throughout the study.

At the conclusion of the study the animal was killed by intravenous injection of KCl, a tourniquet was placed around the neck, and the brain removed via craniectomy. As stated by Risberg *et al.*,<sup>13</sup> the gamma emission measured from the head after removing the brain represents that from extracranial sources. Values for CBV were calculated as the difference between total gamma emission and that representing extracranial sources. To determine relative changes in CBV in the control group, values were normalized to the mean of the CBV values recorded during steady conditions (75 min to 5 h after decreasing the concentration of halothane to <0.1%). To determine relative changes in CBV during prolonged anesthesia, values were normalized to the mean of the values recorded during the pre- and postexposure periods. For the halothane group, steady conditions for preexposure values were taken at 75 min rather than 45–50 min after decreasing the concentration of halothane to <0.1%.

To evaluate the data, cerebral and systemic values in the halothane and enflurane groups were compared with controls using analysis of variance. Where the calculated F value exceeded the critical value for the 0.05 probability level, Tukey's  $\omega$ -procedure was used to determine which differences were significant at  $P < 0.05$ . If at any time period MAP was >150 mmHg, all values (CBV, ICP, and systemic variables) for that time period and subsequent time periods were excluded from the study. When MAP is >150 mmHg, the upper limit of cerebral vascular autoregulation is exceeded, resulting in cerebral vascular distension and possibly cerebral edema or ischemia.<sup>14</sup> Such changes would obscure the effect of anesthesia and CBV on ICP. The relationship between ICP and CBV was examined via both linear regression analysis and least-squares fit for an exponential curve. For these comparisons, ICP values were normalized to those recorded during the preexposure period. The slopes of the regression lines were compared by the F test for homogeneity of regression. Linear regression analysis was used to determine whether CBV,

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ICP, or systemic variables changed with time during prolonged anesthesia. The coefficient of variability was used to determine the relative variability of CBV measurements at each condition. For all statistical comparisons, a value of  $P < 0.05$  was considered significant.

**Results**

Enflurane 2.2% or halothane 0.8% at steady conditions produced a decrease in mean arterial pressure compared with controls (table 1). With halothane, PaO<sub>2</sub> also was decreased compared with controls. Otherwise, there were no significant differences in systemic variables between groups. The only data excluded from the study (due to MAP > 150 mmHg) were from one dog in the enflurane group at the postexposure period.

After 30 min with either halothane or enflurane, both CBV and ICP were increased significantly compared with control values (figs. 1-3). Halothane increased ICP to  $9.8 \pm 1.2$  cmH<sub>2</sub>O and increased CBV by  $11 \pm 1\%$ . Enflurane increased ICP to  $7.9 \pm 1.3$  cmH<sub>2</sub>O and increased CBV by  $8 \pm 1\%$ . With halothane, CBV and ICP remained at stable increased levels until 3.5 h (CBV =  $+12 \pm 2\%$ , ICP =  $9.8 \pm 1.2$  cmH<sub>2</sub>O). Similarly, CBV and ICP remained at stable levels for 3.75 h in controls. With enflurane, while CBV remained at stable increased levels until 3.5 h (CBV =  $+10 \pm 2\%$ ), ICP increased further at  $43 \pm 8$  min compared with 30-min values. ICP increased to  $14.1 \pm 2.2$  cmH<sub>2</sub>O at  $114 \pm 14$  min, then remained at that increased level until 3.5 h. In all groups, CBV, PaO<sub>2</sub>, PaCO<sub>2</sub>, and mean arterial pressure did not change significantly during prolonged anesthesia. When the concentration of enflurane was decreased to <0.2% at the postexposure period, ICP remained increased even though CBV decreased to control values. §

With both halothane and enflurane, the correlation coefficient for the relationship between ICP and CBV was greater for linear regression analysis than for least squares for an exponential curve. For halothane, the linear regression equation was  $y = 6.53(x) + 3.34$  (where  $x = \text{CBV}$  and  $y = \text{ICP}$ , per cent change) with a correlation coefficient of 0.72 ( $P < 0.05$ ). For enflurane, the linear regression equation was  $y = 12.96(x) + 4.54$  (where  $x = \text{CBV}$  and  $y = \text{ICP}$ , per cent change) with a correlation coefficient of 0.39 ( $P > 0.05$ ). The difference in the slopes of the two regression equations did not achieve statistical significance.

Fluctuations in CBV, ICP, and MAP were observed during the first 30-min prolonged anesthesia with either

TABLE 1. Systemic Variables during Prolonged Anesthesia (Mean  $\pm$  SEM)

	Nitrous Oxide (60-70%) and Halothane (<0.1%) in Oxygen (Controls)	Enflurane (2.2%) and Nitrous Oxide (60-70%) in Oxygen	Halothane (0.8%) and Nitrous Oxide (60-70%) in Oxygen
PaO <sub>2</sub> (mmHg)	165 $\pm$ 6	150 $\pm$ 6	141 $\pm$ 6*
PaCO <sub>2</sub> (mmHg)	34 $\pm$ 1	34 $\pm$ 1	34 $\pm$ 1
pH	7.39 $\pm$ 0.02	7.42 $\pm$ 0.02	7.39 $\pm$ 0.02
Bicarbonate (mEq/l)	19.7 $\pm$ 0.7	21.3 $\pm$ 0.8	20.4 $\pm$ 1.0
Hemoglobin (g/dl)	13.8 $\pm$ 0.8	13.2 $\pm$ 0.5	12.3 $\pm$ 0.7
Mean arterial pressure (mmHg)	132 $\pm$ 3	92 $\pm$ 9*	83 $\pm$ 3*
Heart rate (beats/min)	120 $\pm$ 6	107 $\pm$ 5	104 $\pm$ 6
Temperature pharyngeal (°C)	37.1 $\pm$ 0.1	36.9 $\pm$ 0.1	37.0 $\pm$ 0.1

\* Significant difference from control  $P < 0.05$ .

halothane or enflurane (not tabulated). In both groups ICP increased within 1 min, reached peak values at 2-5 min ( $12.7 \pm 0.9$  cmH<sub>2</sub>O in the halothane group,  $12.4 \pm 1.1$  cmH<sub>2</sub>O in the enflurane group), decreased to control values at 7-27 min, then increased to the 30-min values stated above. CBV increased within 1 min, reached peak values at 2-5 min ( $14.3 \pm 1.3\%$  in the halothane group,  $13.6 \pm 1.4\%$  in the enflurane group), then stabilized at the 30-min values stated above. At 2-5 min, MAP was similar to that in the control group, then decreased to stable "anesthetic" values at 6-13 min.

In any animal, measured CBV values varied by  $< \pm 5\%$  from the mean at steady conditions. The coefficient of variability for CBV measurements was 3.3% with halothane, 4.3% with enflurane, and 5.6% during control conditions. Background activity accounted for 7-10% of measured gamma emission. From the determination of residual gamma emission following removal of the brain at the end of the study, it was calculated that 70-75% of measured gamma emission derived from CBV and 15-20% from the extracranial circulation.

**Discussion**

The increases in CBV produced by halothane or enflurane, 11% and 8%, respectively, are less than the increases in CBF previously reported with these anesthetics.<sup>1,7</sup> That changes in CBV are directly related to changes in CBF but are of smaller magnitude is consistent with previous studies that measured CBV and CBF

§ These data exclude values from one dog which during the postexposure period had a mean arterial pressure of 165 mg and ICP of 13 cm (ICP = 5 cmH<sub>2</sub>O at the preexposure period).

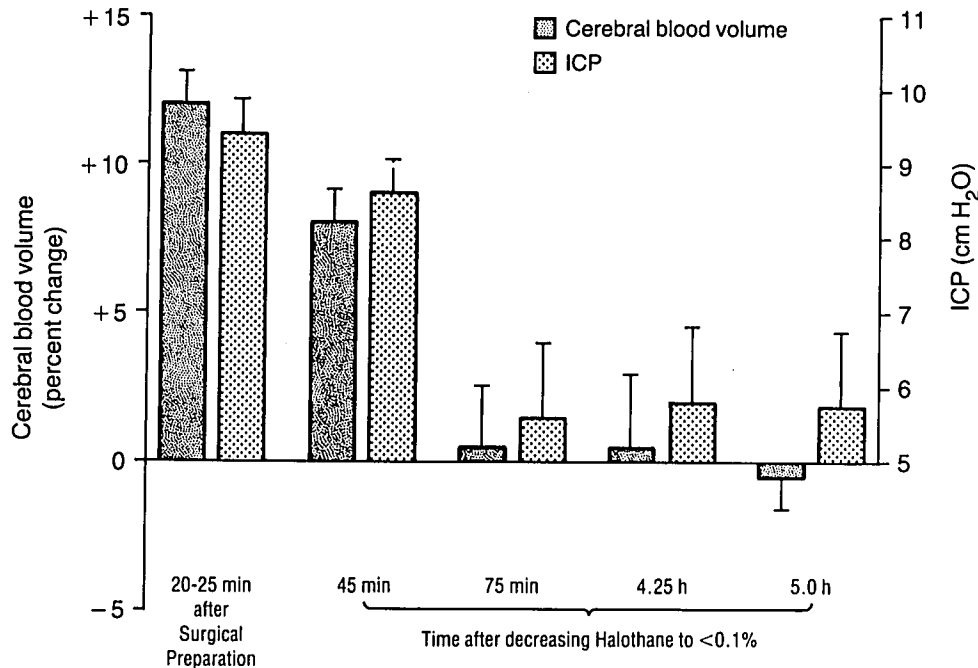


FIG. 1. CBV (solid bars, per cent change from the mean of values at steady conditions) and ICP (stippled bars, cmH<sub>2</sub>O) are shown for the control group. CBV and ICP did not change significantly during steady conditions, 75 min to 5 h after the concentration of halothane was decreased to <0.1%.

simultaneously.<sup>13,15,16</sup> In the present study, the persistent increase in ICP after 30 min 0.8% halothane is in contrast to the results of McDowall *et al.*<sup>17</sup> who reported in dogs anesthetized with halothane no re-occurrence of increased ICP for up to 100 min after ICP had first peaked (3–13 min) then returned to control levels. In

that study, absence of prolonged increased ICP with halothane may relate to the lower concentration of halothane used (0.5%). In the same study McDowall *et al.*<sup>17</sup> reported that in 2/2 dogs ICP increased significantly when the concentration of halothane was increased to 2% after 100 min at 0.5%. Additionally, absence of

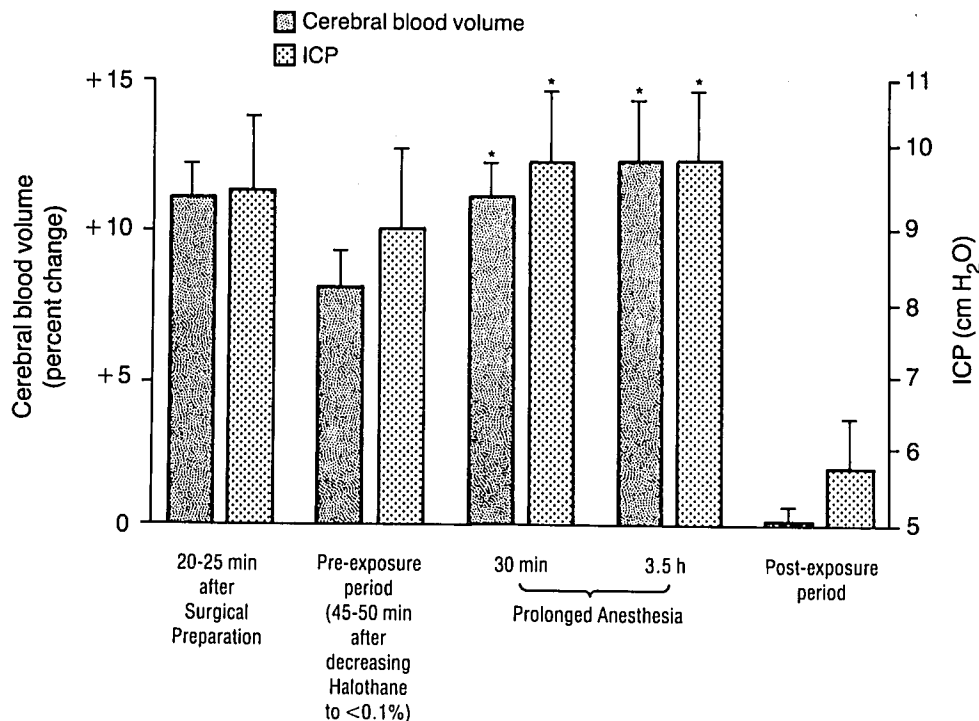
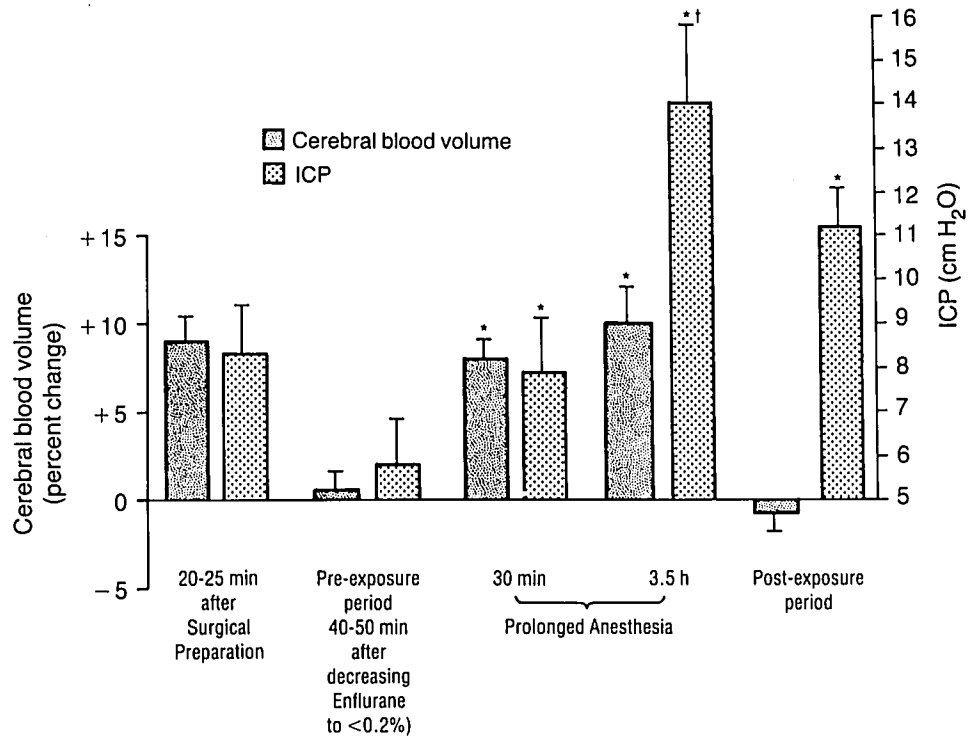


FIG. 2. CBV (solid bars, per cent change) and ICP (stippled bars, cmH<sub>2</sub>O) are shown for the halothane group. During prolonged anesthesia, CBV and ICP were stable and were increased compared with control values. (\*Significantly different from control,  $P < 0.05$ .)

FIG. 3. CBV (solid bars, per cent change) and ICP (stippled bars, cmH<sub>2</sub>O) are shown for the enflurane group. Although CBV remained stable during prolonged anesthesia, ICP increased at 3.5 h compared with 30 min. ICP remained increased in the postexposure period even though CBV decreased to control values. (\*Significantly different from control,  $P < 0.05$ ; †Significantly different from 30-min values during prolonged anesthesia,  $P < 0.05$ .)



prolonged increased ICP with halothane in the study of McDowall *et al.*<sup>17</sup> may relate to the surgical conditions used, *i.e.*, anesthesia with halothane/nitrous oxide/oxygen, cannulation of the sagittal sinus, and ventilation of dogs at a hypercapnic PaCO<sub>2</sub> (44 mmHg). Anesthesia with halothane/nitrous oxide/oxygen plus surgical preparation with sagittal sinus cannulation causes a decrease in CBF of 7–8%/h in dogs.<sup>18</sup> Ventilation at PaCO<sub>2</sub> = 44 mmHg may cause an additional decrease in CBF of 2%/h in dogs due to gradual adjustment of brain extra cellular fluid pH.<sup>19</sup> Thus, in the study of McDowall *et al.*,<sup>17</sup> these effects may have combined to produce a decrease in intracranial volume sufficient to counter any re-occurrence of increased ICP. In the present study, persistent increase of ICP after 30 min 0.8% halothane or 2.2% enflurane suggests that following an initial period of spatial compensation (7–27 min) CSF volume no longer was decreased sufficiently to balance the increase in CBV.

Later increases in ICP with enflurane but not with halothane may relate to anesthetic-induced changes in  $\dot{V}_f$ . Enflurane, which causes a 50% increase in  $\dot{V}_f$  in dogs,<sup>11</sup> produced a delayed increase in ICP during prolonged anesthesia followed by a persistent increased ICP in the postexposure period when the concentration of enflurane was decreased to <0.2%. Neither ICP change was related to CBV. By comparison, halothane, which in dogs causes a prolonged decrease in  $\dot{V}_f$  (author's un-

published data), produced no delayed increase in ICP. Further, the magnitude of the ICP increase observed during prolonged anesthesia with enflurane was consistent with that predicted by previous studies of the relationship between  $\dot{V}_f$  and ICP. The  $\dot{V}_f$ /ICP relationship reported by Bering and Sato<sup>20</sup> in pentobarbital-anesthetized dogs predicts a 6 cmH<sub>2</sub>O increase in ICP for a 50% increase in  $\dot{V}_f$ . The  $\dot{V}_f$ /ICP relationship reported by Pappenheimer *et al.*<sup>21</sup> in unanesthetized goats predicts a 10 cmH<sub>2</sub>O increase in ICP for a 50% increase in  $\dot{V}_f$ . Presumably, increased ICP was not observed in the enflurane group at 20–25 min after surgical preparation because the ventricular and cisternal CSF cannulae used in this study were open-ended when first placed. The duration of exposure to enflurane (2.2%) after the system was “closed” (*i.e.*, the cannulae connected to transducers) was 20–25 min, less than the time required ( $43 \pm 8$  min) for the secondary increase in ICP to occur.

It could be speculated that the increased ICP observed with enflurane resulted not from increased CBV or CSF volume but from an increase in brain tissue volume. In dogs, Smith and Marque<sup>22</sup> reported increased water content in cerebral white matter 24 h following cryogenic lesion in dogs anesthetized with enflurane compared with those anesthetized with pentobarbital or fentanyl–droperidol. However, a similar increase in the water content of cerebral white matter

also was reported in dogs anesthetized with halothane and in "awake" (N<sub>2</sub>O) controls. Thus, it seems unlikely that increased brain tissue volume explains the increased ICP observed here with enflurane compared with halothane or controls.

The initial fluctuations in ICP observed with halothane or enflurane, an early peak followed by a return to control values, were similar to those previously reported by others.<sup>17,23-26</sup> The early peak in ICP may be explained by the overshoot in CBV produced by halothane or enflurane at a time when mean arterial pressure has not yet decreased. The subsequent return of ICP to control values likely reflects a decrease of CSF volume in response to increased CBV.

Regarding the measurement of CBV in the present study, that 25-30% of total gamma emission was found to derive from extracranial sources is consistent with the 30% "background" activity reported by Risberg *et al.* for this technique.<sup>13</sup> In the present study, one-third of this 25-30% extracranial gamma emission derived from true background activity and was constant throughout the study. The remaining two-thirds derived from the systemic extracranial circulation. Although this was only a small part of the total measured gamma emission, it could be argued that in the present study the observed increase in total gamma emission were caused by increases in systemic extracranial blood volume produced by halothane or enflurane rather than increases in CBV. However, in additional studies (author's unpublished studies), it was observed that thiopental, which decreases cerebral blood flow,<sup>27</sup> but like halothane and enflurane increases systemic venous compliance and peripheral venous blood volume,<sup>28</sup> significantly decreased total gamma emission in this model. It therefore seems likely that in the present study the increases in total gamma emission observed with halothane and enflurane derived primarily from CBV rather than systemic extracranial blood volume.

In summary, halothane or enflurane produced increases in CBV that parallel the increase in CBF previously reported with these anesthetics. With halothane, ICP remained increased for 3.5 h and ICP was directly related to CBV. With enflurane, increases in ICP during prolonged anesthesia were not solely related to CBV and may be explained in part by increased  $\dot{V}_f$ . In humans there is indirect evidence that increases in  $\dot{V}_f$  produced by enflurane may contribute to ICP. Hyperventilation reverses the increase in CBF caused by halothane<sup>3</sup> or enflurane,<sup>7</sup> but has no significant effect on  $\dot{V}_f$ .<sup>29</sup> In patients with space occupying intracranial lesions and borderline or increased ICP, hyperventilation minimized increases in ICP produced by halothane<sup>26</sup>

but not those produced by enflurane.<sup>30</sup> These results suggest that with enflurane, increases in ICP were not solely related to CBV and may be due in part to increased  $\dot{V}_f$ .

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