

Enflurane Causes a Prolonged and Reversible Increase in the Rate of CSF Production in the Dog

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Using the open ventriculocisternal perfusion method, rates of cerebrospinal fluid (CSF) production and reabsorption by bulk flow were examined in dogs anesthetized with either enflurane (2.2%) in nitrogen (60–70%) and oxygen, or nitrous oxide (60–70%) and enflurane (<0.2%) in oxygen (controls). The mean rate of CSF production increased significantly with enflurane (2.2%), from 0.055 ± 0.020 ml/min (mean \pm SD) in controls to 0.082 ± 0.033 ml/min ($n = 12$). After this initial increase of approximately 50%, the production rate decreased significantly by about 7.4%/h. When the expired concentration of enflurane was decreased from 2.2% to <0.2%, the mean rate of CSF production decreased to control values at 45–50 min. An intracerebral accumulation of CSF resulting from this enflurane-induced increase in CSF production may contribute in part to increased intracranial pressure when the dura is intact. (Key words: Anesthetics, volatile: enflurane. Brain: intracranial pressure. Cerebrospinal fluid: production; reabsorption.)

TWO RECENT PRELIMINARY REPORTS suggested that enflurane may alter normal CSF dynamics. Meyers and Shapiro§ reported in rats that at enflurane 1.5 MAC,

choroid plexus metabolic rate for glucose was increased from $15 \text{ mg} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ in awake controls to $40 \text{ mg} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, while overall cerebral metabolic rate was decreased approximately 35% from awake values. By comparison, no increase in choroid plexus metabolism was reported with halothane or sodium pentobarbital. On the basis that CSF production is primarily an energy-requiring secretory process, they speculated that the increased choroid plexus metabolic rate seen with enflurane may be accompanied by an increase in the rate of CSF production (\dot{V}_f).

Subsequently, Mann *et al.*¹ examined the effect of enflurane on CSF dynamics in rats using a series of spinal subarachnoid manometric experiments. In those studies, the spinal subarachnoid pressure response to several 8-min infusions of artificial CSF was plotted against the infusion rate, and \dot{V}_f and CSF outflow resistance (resistance to reabsorption) were calculated based on a mathematical model.² They reported that enflurane (1 MAC) significantly increased \dot{V}_f and also increased maximum CSF outflow resistance. With increased resistance to reabsorption of CSF, the rate of CSF reabsorption (\dot{V}_a) may not increase concomitantly with increased \dot{V}_f , causing CSF accumulation. On this basis, the authors speculated that when the dura is intact, CSF accumulation may contribute in part to an increase in intracranial pressure (ICP) as has been observed with enflurane.³ However, it is not known whether this initial increase in \dot{V}_f caused by enflurane persists during prolonged anesthesia. Consequently, the possibility that enflurane causes sufficient CSF accumulation to produce increased ICP remains unproven. Accordingly, the present study was designed to examine the effect of prolonged anesthesia with enflurane on \dot{V}_f in dogs using the classic open ventriculocisternal perfusion method. Also exam-

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§ Meyers RR, Shapiro HM: Paradoxical effect of enflurane on choroid plexus metabolism: Clinical implications (Abstract). American Society of Anesthesiologists 489–490, 1978.

ined was the time required for \dot{V}_f to return to control values when enflurane was decreased to subanesthetic concentrations.

Method

Twenty-one unmedicated fasting mongrel dogs (weights 9–20 kg) were studied. Anesthesia was induced with enflurane (2.2%) and nitrogen (60–70%) in oxygen. Succinylcholine, 30 mg as a bolus injection, followed by infusion of 100 mg/h facilitated endotracheal intubation and maintained muscle relaxation. Ventilation was controlled with a Harvard® pump and adjusted along with the inspired oxygen concentration to maintain serial blood gases (IL electrodes 37° C) at P_{aO_2} of 177 ± 32 mmHg (mean \pm SD) and P_{aCO_2} of 39 ± 1 mmHg.

With the animal in the lateral position, the left femoral vein was cannulated for fluid and drug administration. The left femoral artery was cannulated for arterial blood sampling for blood-gas analysis, determination of buffer base (BB^+), and continuous monitoring of both systemic and mean arterial (MAP) pressures and heart rate. Temperature was monitored by a pharyngeal thermister probe and maintained at $37 \pm 0.5^\circ$ C by heat lamps or ice packs. Depletion of vascular volume was minimized by replacing each ml of sampled blood with 2–3 ml of 0.9% saline.

With the animal in the prone position and the head slightly elevated and fixed on a frame, a scalp incision was made and a burr hole placed 2 cm anterior and 1.5 cm lateral to the external occipital protuberance. After the dura was opened and any bleeding from meningeal vessels controlled with electrocautery, an 18-gauge Teflon® catheter fitted with a blunt tip stylet was directed into the underlying lateral ventricle. The catheter was affixed to the skull and the dura sealed using cyanoacrylate glue.† A 17-gauge stainless steel needle was directed into the cisterna magna following partial dissection of the posterior neck muscles. A short length of 18-gauge flexible tubing was attached to the cisternal needle and the free end was placed at the level of the external auditory meatus. Ventriculocisternal perfusion was begun by infusing through the ventricular catheter mock CSF buffered to pH 7.40 (by bubbling through 5% carbon dioxide in nitrogen). The perfusion rate was controlled with a roller pump and gradually increased to 0.31–0.37 ml/min, while intraventricular pressure was continuously monitored using a Statham strain gauge. After successful ventriculocisternal perfusion was demonstrated, a reference solution of either 50 mg fluoresceine-conjugated albumin** (12 dogs) or 50 mg dextran blue††

(9 dogs) diluted in mock CSF to 100 ml was substituted for mock CSF in the ventricular flow for determination of \dot{V}_f and \dot{V}_a (see appendix). Concentrations of fluoresceine-conjugated albumin were determined using an Aminco Fluoro-colorimeter‡‡ calibrated to 100% using the reference solution and to zero using mixed dog-mock CSF. Concentrations of dextran blue in centrifuged cisternal outflow samples and samples of the reference solution were determined using light absorbance at $610 \mu\text{m}$ on a Beckman DU-2 spectrophotometer§§ (fitted with a Gilford absorbance indicator¶¶).

GROUP 1: ANESTHETIC EFFECT

In 12 dogs, \dot{V}_f and \dot{V}_a were determined during three alternating periods of exposure to either enflurane (2.2%) in nitrogen (60–70%) and oxygen, or nitrous oxide (N_2O) (60–70%) and enflurane (<0.2%) in oxygen (controls). Six dogs received first enflurane, then N_2O , then enflurane; and six dogs received first N_2O , then enflurane, then N_2O . At each condition, successive samples of cisternal outflow solution were collected (5–10 min per sample) and centrifuged. Near steady-state conditions were assumed when measured tracer concentrations in three samples agreed within 2%.

\dot{V}_f and \dot{V}_a were calculated according to the formulas of Heisey *et al.*⁴ (see appendix). Also calculated was the volume of distribution of the tracer substance (VD_x) according to the formula of Pappenheimer *et al.*⁵ (see appendix). Initially, 2–3 h of ventriculocisternal perfusion were allowed for equilibration before determining \dot{V}_f or \dot{V}_a . With each subsequent change in the inspired anesthetic, at least 45 min of perfusion was allowed for elimination of the previous anesthetic and/or establishment of a stable end-expired concentration of the new anesthetic (Beckman LB-2 medical gas analyzer).

GROUP 2: TIME EFFECT

In another six dogs, the effect of time on \dot{V}_f and \dot{V}_a was determined. Three dogs received only enflurane (2.2%) in nitrogen (60–70%) and oxygen, and three received only N_2O (60–70%) and enflurane (<0.2%) in oxygen (controls). Five determinations of \dot{V}_f and \dot{V}_a were made at 45-min intervals beginning 2–3 h after steady-state conditions were achieved.

GROUP 3: N_2O EFFECT

In another three dogs, \dot{V}_f and \dot{V}_a were determined during three alternating periods of exposure to either enflurane (2.2%) in nitrogen (60–70%) and oxygen, or

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§§ Beckman Instruments, Inc., Fullerton, California.

¶¶ Gilford Instrument Laboratories, Inc., Oberlin, Ohio.

enflurane (2.2%) and N₂O (60–70%) in oxygen. In Group 3, to reduce the potential for trauma to the dorsal brain stem and spinal cord, posterior neck muscles were completely dissected free from the midline and a fine-tipped tapered glass cannula was directed through the dura into the cisterna magna to collect CSF outflow rather than a 17-gauge stainless steel needle.

At the conclusion of all studies, animals were killed by intravenous injection of potassium chloride. The brain was removed for inspection and the choroid plexus dissected free for inspection and weighing.

To determine whether \dot{V}_f and \dot{V}_a changed with time, either during enflurane or in controls, linear regression analysis was done on normalized values from the 18 animals exposed to enflurane (2.2%) in nitrogen (60–70%) and oxygen, and/or N₂O (60–70%) and enflurane (<0.2%) in oxygen, and the correlation coefficient was computed. When a time effect was significant, CSF values were time-corrected prior to computing the mean and SD. Systemic variables and CSF values during enflurane were compared to controls using Student's *t* test for paired samples. Values in Group 2 and Group 3 were not compared statistically due to the small number in each group.

Results

Values for \dot{V}_f and systemic variables did not differ between groups using either fluoresceine-conjugated albumin or dextran blue as the tracer, and were therefore combined. Both MAP and heart rate decreased during anesthesia with enflurane compared to N₂O controls (table 1). Otherwise, systemic variables were similar during anesthesia with enflurane/nitrogen or enflurane/N₂O and in N₂O controls. \dot{V}_f increased significantly (49%) during enflurane compared with controls (table 2). This increase in \dot{V}_f was to 0.074 ± 0.013 ml/min from 0.050 ± 0.012 ml/min when dextran blue was used as the tracer, and to 0.089 ± 0.034 ml/min from 0.061 ± 0.026 ml/min when fluoresceine was used as the tracer. This enflurane-induced increase was greatest at the first measurable time period and, based on the slope of the regression line, \dot{V}_f decreased thereafter at about 7.4%/h during anesthesia with enflurane (fig. 1). Thus, \dot{V}_f during enflurane was increased significantly compared with controls for 5–5.5 h before decreasing to control values. The normalized regression line for \dot{V}_f during anesthesia with enflurane was $99 - 0.124(x)$ per cent/min, where *x* = time (min; *r* = 0.85, significantly different from 0 at *P* < 0.001). The normalized regression line for \dot{V}_f in N₂O controls was $90 - 0.068(x)$ per cent/min, where *x* = time (min; *r* = 0.39, not significantly different from 0). The steady-state rate of CSF outflow from the cisternal collecting cannula increased during enflurane to 0.370 ± 0.028 ml/min from 0.323 ± 0.028

TABLE 1. Effects of Enflurane on Systemic Variables (mean \pm SD)

	Anesthetic Effect (n = 12)	
	N ₂ O (60–70%) and Enflurane (<0.2%) in Oxygen (Controls)	Enflurane (2.2%) in Nitrogen (60–70%) and Oxygen
PaO ₂ (mmHg)	176 \pm 40	168 \pm 48
PaCO ₂ (mmHg)	38 \pm 1	38 \pm 1
pH	73.9 \pm 0.03	7.40 \pm 0.02
BB* (mEq/l)	43 \pm 1	44 \pm 1
Hemoglobin (g/dl)	13.5 \pm 2.0	12.4 \pm 1.5
Mean arterial pressure (mmHg)	117 \pm 23	74 \pm 16*
Heart rate (beats/min)	129 \pm 23	108 \pm 20*
Temperature, pharyngeal (°C)	37.2 \pm 0.2	37.0 \pm 0.3

BB* = Buffer base.

* Significant difference from control, *P* < 0.05.

ml/min in controls (*P* < 0.01 by Student's *t* test for paired samples). Other cerebral variables were not significantly different during enflurane compared to N₂O controls (table 2). The normalized regression lines for other cerebral variables either during anesthesia with enflurane or in N₂O controls were not significantly different from 0.

In the studies of anesthetic effect, \dot{V}_f decreased to control values at 45–50 min when the end-expired concentration of enflurane was decreased from 2.2% to <0.2%. In the studies of time effect, \dot{V}_f increased by 56% during enflurane compared to N₂O controls. In the studies comparing enflurane/N₂O to enflurane/nitrogen, \dot{V}_f was not changed significantly (mean \dot{V}_f decreased by 2%) when N₂O was substituted for nitrogen in the inspired gases. In none of the groups were other cerebral variables significantly different during enflurane compared to N₂O controls (not tabulated). While a statistically significant change in mean ICP did not occur in any of the groups during the study, increased ICP during the latter part

TABLE 2. Effects of Enflurane on Cerebral Variables (mean \pm SD)

	Anesthetic Effect (n = 12)	
	N ₂ O (60–70%) and Enflurane (<0.2%) in Oxygen (Controls)	Enflurane (2.2%) in Nitrogen (60–70%) and Oxygen
\dot{V}_f (ml/min)	0.055 \pm 0.020	0.082 \pm 0.033*
CSF intraventricular pressure (mmHg)	7.3 \pm 2.5	8.0 \pm 2.2
Perfusion rate (ml/min)	0.33 \pm 0.05	0.33 \pm 0.05
Choroid plexus weight (mg)	80 \pm 25	80 \pm 25
VD _x (ml)	6.77 \pm 1.08	6.77 \pm 1.08

\dot{V}_f = the rate of CSF production. VD_x = volume of distribution of the tracer substance.

* Significant difference from control, *P* < 0.05.

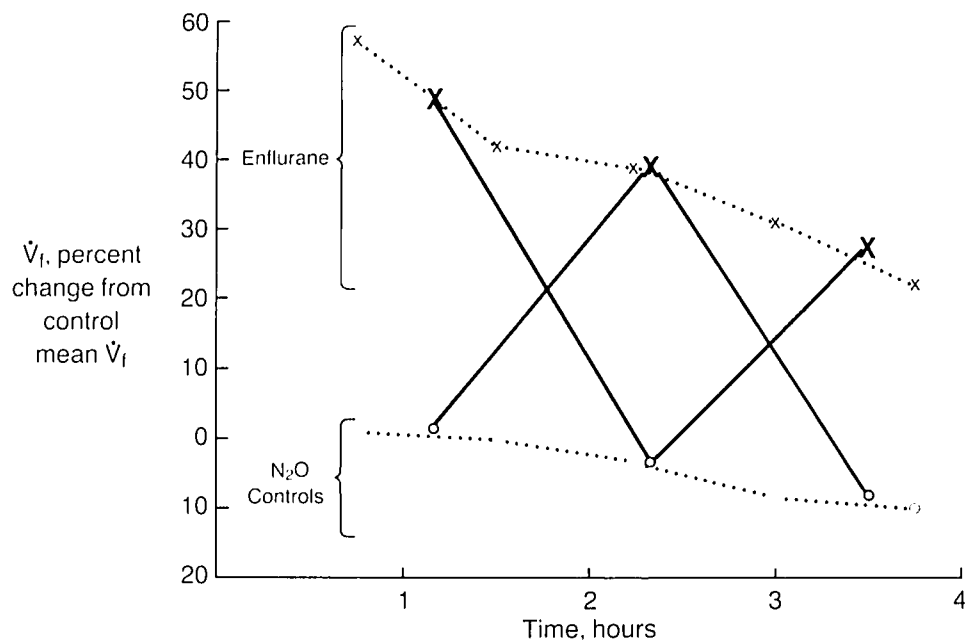


FIG. 1. \dot{V}_f values during alternating exposure to either enflurane- N_2O -enflurane (\times — \circ — \times , $n = 6$) or N_2O -enflurane- N_2O (\circ — \times — \circ , $n = 6$) and during anesthesia with enflurane at five intervals ($\times \cdots \times$, $n = 3$) or N_2O at five intervals ($\circ \cdots \circ$, $n = 3$). \dot{V}_f is expressed as per cent change from control mean \dot{V}_f , and time refers to hours elapsed following surgical preparation and tracer equilibration.

of the study was observed in one dog in Group 1 and three dogs in Group 2 (fig. 2). Excluding these dogs, mean \dot{V}_a during enflurane was 0.047 ± 0.038 ml/min, and mean \dot{V}_a in N_2O controls was 0.051 ± 0.036 ml/min. In none of the groups was there visible evidence of cerebral edema or choroid plexus abnormality. The mean choroid plexus weight for all dogs was 83 ± 26 mg. VD_x for the fluoresceine-conjugated albumin tracer ranged from 6.91 ± 0.46 ml to 7.39 ± 0.16 ml. VD_x for the dextran blue tracer ranged from 6.49 ± 0.11 ml to 6.64 ± 0.10 ml. At perfusion rates of 0.31–0.37 ml/min, stable concentrations of tracer substance were measured at 45 min after each change in the inspired anesthetic. The duration of these studies was 334 ± 14 min.

Discussion

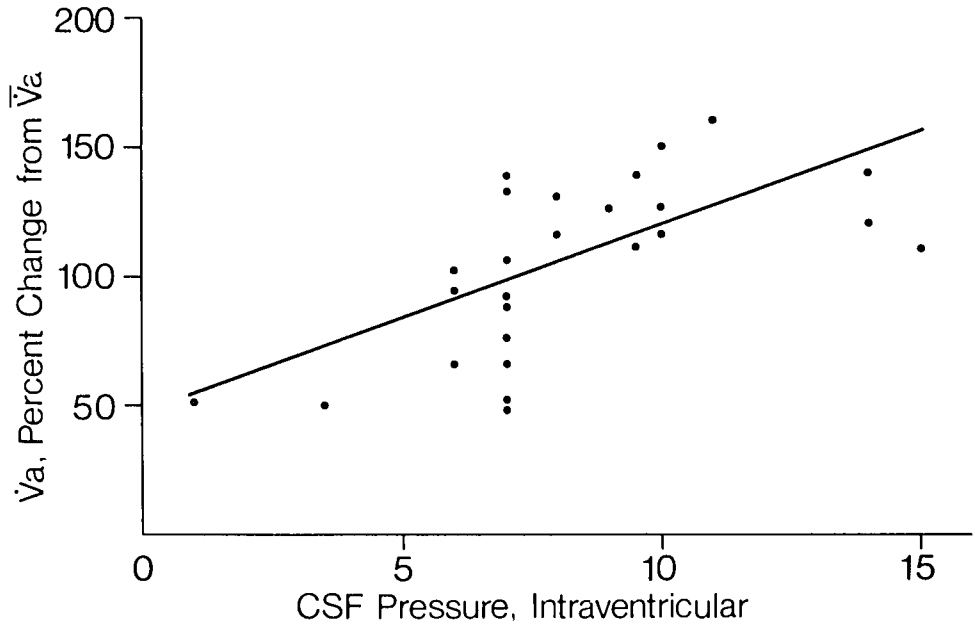
Several observations support our use of N_2O as an appropriate anesthetic for control measurements of \dot{V}_f and \dot{V}_a . In previous studies from this laboratory,⁶ it was found that \dot{V}_f during anesthesia with nitrous oxide (60–70%) and enflurane (<0.2%) in oxygen was 0.048 ± 0.014 ml/min, a value in excellent agreement with canine values for \dot{V}_f previously reported as “control” or “awake” by others (0.035 – 0.069 ml/min^{7–13}). In the present study, \dot{V}_f in controls anesthetized with N_2O (60–70%) and enflurane (<0.2%) in oxygen was 0.055 ± 0.020 ml/min ($n = 15$), a value similar to that reported for dogs in previous studies in this laboratory⁶ and by others.^{7–13} Further, substituting N_2O (60–70%) for nitrogen (60–70%) in dogs receiving enflurane 2.2% in oxygen produced no significant change in \dot{V}_f or \dot{V}_a . Finally, in additional studies from this laboratory, \dot{V}_f and \dot{V}_a during anesthesia with N_2O (60–70%) and enflurane

(<0.2%) in oxygen were not significantly different from \dot{V}_f and \dot{V}_a during anesthesia with N_2O (60–70%) and halothane (<0.1%) in oxygen (authors’ unpublished studies). Our results in controls also suggest that significant physiologic deterioration of this preparation did not occur with time. In our controls, the decrease in \dot{V}_f with time suggested by the regression line, $2.4 \mu\text{l} \cdot \text{min}^{-1} \cdot \text{h}^{-1}$ was not statistically significant and was in excellent agreement with the time-related decrease in \dot{V}_f in controls previously reported by Martins *et al.* for ventriculocisternal perfusion studies in monkeys, $2.3 \mu\text{l} \cdot \text{min}^{-1} \cdot \text{h}^{-1}$.¹⁴

The use of two different tracers in this study is accounted for by a previous study in which we attempted to determine the effects of enflurane on CSF dynamics using a new method of closed recirculatory spinal subarachnoid perfusion.⁶ In that study, we used fluoresceine-conjugated albumin in order to apply the method as originally described. However, because of considerable variability in results, we failed to document any effect of enflurane, and instead determined some of the various factors that contributed to the variability that was encountered with that method. In the present study, we used the classical open ventriculocisternal perfusion technique to address the same question. This provided an opportunity to evaluate the degree to which fluoresceine-conjugated albumin may have contributed to the variability encountered in the original study. The results indicate that whether using the more common tracer, dextran blue, or fluoresceine-conjugated albumin, a demonstrable and similar effect of enflurane on CSF dynamics can be readily determined using open ventriculocisternal perfusion.

In the present study, the 49% increase in \dot{V}_f we ob-

FIG. 2. \dot{V}_a values during anesthesia with either enflurane or N_2O (Groups 1 and 2), expressed as per cent change from \dot{V}_a for each anesthetic, are plotted as a function of intraventricular CSF pressure (mmHg). The line of regression fits the equation $y = 6.8(x) + 48$ (where y = per cent change in \dot{V}_a , and x = intraventricular CSF pressure) and is in good agreement with the data of both Bering and Sato⁹ in pentobarbital-anesthetized dogs and Heisey *et al.*⁴ in unanesthetized goats. For this equation, $r = 0.64$, significantly different from 0 at $P < 0.01$.



served with enflurane was measured after prolonged anesthesia with enflurane for surgical preparation and for 2–3 h of tracer equilibration. In a previous study, a near 100% increase in \dot{V}_f was derived by Mann *et al.* in short-term studies in rats during anesthesia with enflurane (1 MAC) using an indirect mathematical model.¹ The results of our study and that of Mann *et al.*¹ are in good agreement considering the differences in duration of exposure to enflurane and our observation of a 7.4%/h decrease in enflurane-stimulated \dot{V}_f after our first measurement period. While the cause(s) of this significant initial increase in \dot{V}_f (and subsequent slow return to control levels) are unknown, we speculate that the paradoxical increase in choroid plexus metabolism previously reported for enflurane*** is directly related to this observation. As regards ICP, the increased \dot{V}_f caused by enflurane persists for a sufficient amount of time that an increase in ICP should result. The \dot{V}_f /ICP relationship reported by Bering and Sato⁹ during prolonged pentobarbital anesthesia in dogs predicts an increase in ICP to 13.4 cmH₂O from 7 cmH₂O when \dot{V}_f is increased by 50%. The \dot{V}_f /ICP relationship reported by Pappenheimer *et al.*⁵ in unanesthetized goats predicts an increase in ICP to 17.4 cmH₂O from 7 cmH₂O when \dot{V}_f is increased by 50%.

The magnitude of the ICP increase produced by increased \dot{V}_f is limited by the fact that \dot{V}_a increases proportionately in response to increased ICP, while \dot{V}_f is not affected by ICP.^{9,15} Thus, ICP would rise only until \dot{V}_a increased sufficiently to match \dot{V}_f . In the present

study, because the cisterna magna cannula collecting CSF outflow is open ended, intracranial volume did not increase. Instead, the imbalance between \dot{V}_f and \dot{V}_a caused by enflurane was reflected by an increase in the steady-state rate of CSF outflow. A high value for \dot{V}_a would occur if CSF pressure was increased, if CSF was redistributed to the spinal subarachnoid space, or if tracer adherence was occurring in the spinal subarachnoid space. While in the present study neither redistribution of CSF or tracer adherence was measurable, increased ICP occurred in four dogs in Groups 1 and 2 during the latter stages of the study, apparently due to accumulation of CSF debris at the indwelling tip of the outflow cannula. Because \dot{V}_a is proportional to intraventricular CSF pressure,^{4,9,15} increased ICP in these animals resulted in increased mean \dot{V}_a for the group despite statistically unchanged ICP (fig. 2). By comparison, \dot{V}_f is unaffected by intraventricular CSF pressure.^{9,15}

A number of systemic variables, *i.e.*, MAP,¹² pH,^{8,14} temperature,^{16,17} and PaO₂,¹⁸ have been reported previously to significantly affect \dot{V}_f . In the present studies these variables were sufficiently controlled as to have minimal effects on \dot{V}_f . The exception was MAP which was reduced to 74 ± 16 mmHg (n = 12) during enflurane. However, this MAP is well above the MAP (62 ± 1 mmHg, mean ± SEM) at which Carey and Vela reported that phlebotomy-induced hypotension produced a 39% decrease in \dot{V}_f in pentobarbital-anesthetized dogs.¹² Furthermore, we observed an increase in \dot{V}_f at a time that MAP was decreased. Thus, it seems unlikely that any alteration in systemic variables significantly affected \dot{V}_f .

While radioiodinated human serum albumin (RISA) and dextran blue have commonly been used for ventricu-

*** Meyers RR, Shapiro HM: Paradoxical effect of enflurane on choroid plexus metabolism: Clinical implications (Abstract). American Society of Anesthesiologists 489–490, 1978.

locisternal perfusion studies, the use of fluoresceine-conjugated albumin has not, to our knowledge, been previously reported. That results similar to those in our fluoresceine studies were observed in our dextran blue studies suggests that while fluoresceine-conjugated albumin is suitable for determination of qualitative changes in CSF dynamics using this model, it may not be the ideal tracer. Control \dot{V}_f values obtained using fluoresceine as the tracer substance tended to be increased, though not statistically different compared with those obtained using dextran blue. Further control \dot{V}_f values using fluoresceine were higher than those previously reported in dogs using ventriculocisternal perfusion in all studies except one.⁷⁻¹³ By comparison, the VD_x of the fluoresceine-conjugated albumin and dextran blue was similar to that reported in dogs for RISA (5.2 ml) and urea (7.6 ml) by Bering and Sato.⁹ The choroid plexus weights reported here are similar to those reported in other canine studies.⁹

In summary, enflurane (2.2%) was observed to significantly increase \dot{V}_f in dogs. The increase was greatest initially and remained increased compared to controls for 5-5.5 h during enflurane anesthesia. The increase in \dot{V}_f was reversed within 50 min after decreasing the expired concentration of enflurane from 2.2% to <0.2%. During prolonged enflurane anesthesia, increased \dot{V}_f persists for sufficient time to produce increased ICP when the dura is intact, and work is currently in progress to examine this effect in the "closed" skull.

APPENDIX

Ventriculocisternal perfusion is an open perfusion technique employing a nondiffusible tracer substance which is removed primarily by bulk absorption of CSF. Tracer-laden mock CSF is infused into a lateral cerebral ventricle and collected from the cisterna magna.^{12,13} \dot{V}_f is then calculated by determining the dilution of the tracer substance by newly formed CSF, and \dot{V}_a is calculated by determining tracer clearance. This method has been accepted for years as a reliable and precise means for determining \dot{V}_f and \dot{V}_a . In addition, this method allows the determination of \dot{V}_f and \dot{V}_a over a clinically relevant interval of several hours.

\dot{V}_f was calculated according to the formula:

$$\dot{V}_f = \dot{V}_i \left(\frac{C_i - C_o}{C_o} \right)$$

where \dot{V}_i is the inflow rate of the reference solution, C_i is the inflow concentration of the tracer substance, and C_o is the outflow concentration of the tracer substance. \dot{V}_a was calculated by the formula:

$$\dot{V}_a = \frac{\dot{V}_i C_i - \dot{V}_o C_o}{C_o}$$

where \dot{V}_o is the rate of outflow of mixed CSF and reference solution at the cisterna magna. VD_x was calculated by the for-

mula:

$$VD_x = \frac{\sum_0^n [\dot{V}_i C_i - \dot{V}_o C_o - C_x \bar{C}_o(t)] \Delta t}{\bar{C}}$$

where C_x is the steady-state clearance of $x = \dot{V}_i C_i - \dot{V}_o C_o / \bar{C}$, $\bar{C}_o(t)$ is C_o at steady-state conditions, and \bar{C} is the mean concentration in the ventricular system = $C_o + 0.37(C_i - C_o)$ as stated by Pappenheimer *et al.*¹⁹

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