Effects of Enflurane and Isoflurane on Resistance to Reabsorption of Cerebrospinal Fluid in Dogs

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Using the technique of ventriculocisternal perfusion, resistance to reabsorption of cerebrospinal fluid (Rw) was calculated from determinations of the rate of reabsorption of cerebrospinal fluid (Vr) at differing cerebrospinal fluid pressures in dogs. Rw was examined during prolonged anesthesia (5.0–6.0 h) with enflurane (2.2%, end expired) or isoflurane (1.4%, end expired). Compared with previously reported normal values for Rw in dogs (220–224 cmH2O·ml⁻¹·min⁻¹), enflurane increased Rw to 274 ± 4 cmH2O·ml⁻¹·min⁻¹ (mean ± SEM), and isoflurane decreased Rw to 104 ± 1 cmH2O·ml⁻¹·min⁻¹. The alterations of cerebrospinal fluid (CSF) dynamics caused by enflurane, namely increase of both Rw and the rate of production of cerebrospinal fluid (VR), may contribute to the sustained increase of intracranial pressure observed during prolonged anesthesia with enflurane. In contrast, the different alterations of CSF dynamics caused by isoflurane, namely decrease of Rw with no change in VR, may explain, in part, why minimal increase of intracranial pressure is observed during prolonged anesthesia with isoflurane. Because decreased Rw improves spatial compensation by cerebrospinal fluid volume for increased intracranial pressure, isoflurane may offer an advantage over enflurane in patients at risk because of increased intracranial pressure. (Key words: Anesthetics, volatile: enflurane, isoflurane. Brain: intracranial pressure. Cerebrospinal fluid: reabsorption production.)

DURING PROLONGED enflurane anesthesia (3.5 h), a late-occurring, sustained increase of cerebrospinal fluid (CSF) pressure has been observed in dogs.1 Unlike the early, transient increase of CSF pressure associated with enflurane anesthesia,1 the later, sustained increase could not be explained solely by an increase in cerebral blood volume.1 The later increase of CSF pressure may result in part from an increase in CSF volume because of an increase in the rate of CSF production (VR). Artru et al. reported in dogs that enflurane (2.2%, end expired) caused a 50% increase in VR after 2 h enflurane anesthesia.2 However, VR decreased by ~7%/h thereafter, so increased VR alone could not account for a sustained increase of CSF pressure over 3.5 h enflurane anesthesia. Previously, Mann et al. reported in rats that when data on lumbar CSF pressure during several-minute infusions of mock CSF into the lumbar CSF space were fit to a mathematical model,3,4 resistance to reabsorption of CSF (Rw) was greater during anesthesia with enflurane (2.5%) than during the control state of pentobarbital anesthesia (40 mg/kg, intraperitoneally).5 Thus, it may be that the late occurring, sustained increase of CSF pressure observed during prolonged enflurane anesthesia in dogs results in part from an increase in CSF volume because of increased Rw. However, whether the increase in Rw observed during the short-term studies persists during prolonged enflurane anesthesia is not known.

Accordingly, the present study was designed to examine the effect of prolonged enflurane anesthesia on Rw in the dog. Also examined was the effect on Rw of prolonged isoflurane anesthesia, an anesthetic that exhibits no late-occurring increase in CSF pressure.6

Methods

Twelve unmedicated mongrel dogs (weights 10–20 kg) were studied. Six dogs were anesthetized with enflurane (>2.5%, inspired) and nitrous oxide (N₂O, 60–70%) in oxygen, and six dogs were anesthetized with isoflurane (>1.8%, inspired) and N₂O (60–70%) in 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 gas tensions (Radiometer BMS® MK2 electrodes) to Pao₂ > 120 mmHg and Paco₂ 35 ± 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 succinylcholine 50–120 μg/kg maintained muscle relaxation. The right femoral artery was cannulated for arterial blood sampling for blood gas analysis and continuous monitoring of systemic arterial blood pressure and heart rate. Mean arterial pressure (MAP) was determined by electronic integration. Expired CO₂ continuously was monitored using a Beckman LB-2® Medical Gas Analyzer. Temperature was monitored by an esophageal thermister probe and maintained at 37.0 ± 0.5°C by heat lamps or ice packs. Depletion of vascular volume was minimized by continuous infusion of saline 4–6 ml·kg⁻¹·h⁻¹.

With the animal in the prone position and the head slightly elevated and fixed on a stereotaxic frame, cannuiae were placed into a lateral cerebral ventricle and into the cisterna magna as previously described.7 The burr hole for the ventricular cannula was sealed and the cannula affixed to the skull using methyl methacrylate.

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Table 1. Combined Systemic Variables from Four CSF Pressures (Control, +5, +10, and +15 cmH2O) (Mean ± SEM)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Enflurane (2.2%)* and N2O (60-70%) in O2 (n = 6)</th>
<th>Isoflurane (1.4%)* and N2O (60-70%) in O2 (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ptas (mmHg)</td>
<td>132 ± 4</td>
<td>154 ± 2†</td>
</tr>
<tr>
<td>Ptcbl (mmHg)</td>
<td>36 ± 1</td>
<td>35 ± 1</td>
</tr>
<tr>
<td>pH</td>
<td>7.41 ± 0.01</td>
<td>7.42 ± 0.01</td>
</tr>
<tr>
<td>Bicarbonate (mEq/l)</td>
<td>22.7 ± 0.4</td>
<td>21.8 ± 0.5</td>
</tr>
<tr>
<td>Glucose, plasma (mg/dl)</td>
<td>115 ± 5</td>
<td>121 ± 4</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.2 ± 0.4</td>
<td>12.0 ± 0.4</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>95 ± 5</td>
<td>108 ± 4†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>92 ± 3</td>
<td>124 ± 9†</td>
</tr>
<tr>
<td>Temperature, pharyngeal (°C)</td>
<td>-36.9 ± 0.1</td>
<td>37.0 ± 0.1</td>
</tr>
</tbody>
</table>

* End-expired value.
† Significant difference from enflurane (2.2%), P < 0.05.

resin (Nuwele®, the L. D. Caulk Company, Milford, Delaware). A T-connector was attached to the ventricular cannula, and ventricular CSF pressure was measured by connecting one arm of the cannula T-connector to a strain gauge transducer (Statham® P 23 AA) via a short length of fine nylon tubing. The level of the external auditory meatus was used as the zero reference for CSF pressure measurement. A 0.5-ml sample of dog CSF was obtained from the cisternal cannula for measurement of osmolality using a Wescor Model 5100 B Vapor Pressure Osmometer® (Wescor, Inc., Logan, Utah). Mock CSF of matching osmolality was prepared by mixing standard solutions® (osmolality 290, 300, or 310 mOs/kg) labeled with blue dextran (1 mg/ml) (Sigma Chemical Co., St. Louis, Missouri).

Ventriculocisternal perfusion was begun by infusing through the second arm of the T-connector of the ventricular cannula labeled mock CSF buffered to pH 7.40 by equilibration with 5% carbon dioxide in oxygen. The perfusion rate, controlled with a roller pump, gradually was increased to 0.3 ml/min, while ventricular CSF pressure was monitored continuously. Successful ventriculocisternal perfusion was indicated by outflow of labeled CSF from the cisternal cannula with no increase in CSF pressure above preperfusion values. In the six dogs surgically prepared under enflurane anesthesia, the concentration of enflurane was decreased to 2.2% (end-expired value determined by gas chromatography) in N2O (60-70%) and oxygen. In the six dogs surgically prepared under isoflurane anesthesia, the concentration of isoflurane was decreased to 1.4% in N2O (60-70%) and oxygen. For both groups, 2-5 h of ventriculocisternal perfusion was allowed for equilibration of the labeled mock CSF with native dog CSF in the intracerebral CSF spaces of the dog. Steady state condition were assumed when tracer concentrations in three consecutive samples of cisternal outflow agreed within 2%. Concentrations of blue dextran in centrifuged cisternal outflow samples and samples of the labeled mock CSF perfused into the ventricle were determined using light absorbance at 610 nm on a Beckman DU-28 spectrophotometer (Beckman Instruments, Inc., Fullerton, California) (fitted with a Gilford absorbance indicator [Gilford Instrument Laboratories, Inc., Oberlin, Ohio]).

Following equilibration of the tracer, Rv was determined for each dog. By definition, Rv is a reciprocal measure of the slope relating the rate of reabsorption of CSF (Vv) (ml/min) to CSF pressure (cmH2O). Thus, Rv, expressed as cmH2O · ml⁻¹ · min⁻¹, is a calculated value derived as the reciprocal of the Vv/CSF pressure slope. In the present study the Vv/CSF pressure slope was obtained by determining Vv at four CSF pressures: first at preperfusion CSF pressure (control conditions), then at 5, 10, and 15 cmH2O above control values. Vv was calculated as previously described, according to the formula of Heisey et al., by determining tracer clearance. Increases of CSF pressure were achieved by elevating the tip of the cisternal outflow cannula. Various orders of increased CSF pressure were used so that within each group of dogs all possible combinations of increased CSF pressure were tested. At least 45 min of perfusion was allowed at each CSF pressure to reestablish steady state conditions. Also determined at each of the four CSF pressures was Vf (calculated as previously described), the volume of distribution of the tracer substance (Vd, calculated according to the formula of Pappenheimer et al.), and systemic variables. 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.

In both the enflurane and isoflurane groups, mean systemic and CSF values at increased CSF pressures (+5 cmH2O, +10 cmH2O, and +15 cmH2O) were compared with their respective control values using repeated-measures analysis of variance. Where the calculated F value exceeded the critical value for the 0.05 probability level, a paired t test with the Bonferroni correction was used to determine which treatment differences were significant at P < 0.05. Data between groups were analyzed using one way analysis of variance. The relationship between CSF pressure and both Vv and Vf was determined by linear regression analysis and computation of the correlation coefficient. Difference in regression slopes between groups was determined by the F test for homogeneity of regression. For all statistical comparisons, a P value of less than 0.05 was considered significant.
Results

During both enflurane or isoflurane anesthesia, systemic variables did not change significantly as CSF pressure was increased. Mean values for each of the four levels of CSF pressure (control, +5 cmH2O, +10 cmH2O, and +15 cmH2O) therefore were combined (table 1). Mean values for systemic variables during enflurane were not significantly different from those during isoflurane anesthesia except for heart rate, mean arterial pressure, and PaO2, which were increased during isoflurane.

During enflurane anesthesia, $\dot{V}_a$ increased as CSF pressure was increased (fig. 1), and $R_a$ was $274 \pm 4$ cmH2O·ml⁻¹·min (mean ± SEM). The regression line for $\dot{V}_a$ was $y = 0.0037 (x) + 0.0277$ (where $x$ = CSF pressure, cmH2O above control CSF pressure, and $y$ = $\dot{V}_a$, ml/min) with a correlation coefficient of 0.59 ($P < 0.05$). $\dot{V}_f$ at increased CSF pressures (+5, +10, and +15 cmH2O) was not significantly different (mean $\dot{V}_f$ = $0.053 \pm 0.008$ ml/min) from control $\dot{V}_f$ (0.063 ± 0.012 ml/min, fig. 2).

During isoflurane anesthesia, $\dot{V}_a$ increased as CSF pressure was increased (fig. 1). $R_a$ during isoflurane anesthesia was $104 \pm 1$ cmH2O·ml⁻¹·min, significantly less than $R_a$ during enflurane anesthesia. The regression line for $\dot{V}_a$ was $y = 0.0096 (x) + 0.0102$ (where $x$ = CSF pressure, cmH2O above control CSF pressure, and $y$ = $\dot{V}_a$, ml/min) with a correlation coefficient of 0.79 ($P < 0.05$). The regression line for $\dot{V}_a$ during isoflurane was significantly different from that during enflurane. During isoflurane, $\dot{V}_f$ did not change significantly as CSF pressure was increased (fig. 2), and control $\dot{V}_f$ values were less than control $\dot{V}_f$ values during enflurane (table 2). The mean $\dot{V}_f$ value combined from the $\dot{V}_f$ values at each of the four levels of CSF pressure was $0.037 \pm 0.007$ ml/min with isoflurane anesthesia.

Other cerebral variables, i.e., CSF pressure during control conditions, CSF osmolality, perfusion rate of mock CSF, and $V_{Dx}$, were not significantly different during enflurane anesthesia from those during isoflurane anesthesia (table 2). In none of the dogs was there visible evidence of cerebral edema or choroid plexus abnormality. The mean duration of ventriculocisternal perfusion was $328 \pm 14$ min.
Table 2. Control Cerebral Variables (Mean ± SEM)

|                      | Enflurane (2.2%*) and N2O (60-70%)
|                      | in C4 (n = 6)                      | Isoflurane (1.4%*) and N2O (60-70%)
|                      | in C4 (n = 6)                      |
|----------------------|-----------------------------------|-----------------------------------|
| $V_f$ (ml/min)       | 0.083 ± 0.005                      | 0.040 ± 0.002†                    |
| $V_a$ (ml/min)       | 0.033 ± 0.004                      | 0.011 ± 0.002                     |
| CSF pressure,        |                                   |                                   |
| intraventricular      | 7.3 ± 0.4                          | 7.0 ± 0.9                         |
| (cmH2O)              |                                   |                                   |
| CSF osmolality        | 301 ± 2                            | 305 ± 3                           |
| (mOsm/kg)            |                                   |                                   |
| Perfusion rate (ml/min)| 0.31 ± 0.01                       | 0.30 ± 0.01                       |
| $VD_i$ (ml)          | 6.64 ± 0.10                        | 6.54 ± 0.19                       |

$V_f$ = the rate of CSF production; $V_a$ = the rate of CSF reabsorption; $VD_i$ = volume of distribution of the tracer substance.

* End-expired value.
† Significant difference from enflurane (2.2%), $P < 0.05$.

Discussion

That differences exist between anesthetics regarding their effects on $R_a$ is of interest because $R_a$ plays a crucial role in the regulation of intracranial pressure (ICP). ICP is determined by the volumes of the three intracranial compartments: cerebral blood volume (CBV), brain tissue volume, and CSF volume. When either CBV or brain tissue volume expand, ICP initially increases due to the poor distensibility of the skull and meninges. If $R_a$ and $V_f$ are unchanged, ICP increase causes CSF volume to decrease resulting in a return of ICP to normal levels. However, if $R_a$ and/or $V_f$ are increased, ICP stabilizes at elevated levels. Thus, within the limits of CSF volume to decrease to accommodate increases in CBV or brain tissue volume, global (though not necessarily regional) ICP is determined solely by the balance between $R_a$ and $V_f$.

In the present study, $R_a$ during enflurane anesthesia (274 ± 4 cmH2O·ml⁻¹·min) was higher than previously reported normal $R_a$ values for dog (220–224 cmH2O·ml⁻¹·min) obtained during anesthesia with pentobarbital. Enflurane previously was reported to increase $V_f$. This increase of $R_a$ and $V_f$ by enflurane may explain in part the observation in dogs that when enflurane (2.2%) is administered, the resulting increase of CBV is not compensated for, but instead causes a sustained (3.5 h) increase of ICP. The proposal that anesthetic-induced alteration of $R_a$ plays a role in the regulation of ICP also is consistent with studies of halothane anesthesia in dogs. Halothane, which causes less increase in $R_a$ than enflurane, but a similar increase in CBV to enflurane, is accompanied by a sustained increase of ICP smaller in magnitude than that observed with enflurane.

In contrast to enflurane, $R_a$ during isoflurane anesthesia (104 ± 1 cmH2O·ml⁻¹·min) was lower than previously reported normal $R_a$ values for dog. Isoflurane previously was reported to produce no change in $V_f$ in dogs. That isoflurane decreases $R_a$ and does not alter $V_f$ may explain in part the observation that no sustained increase of ICP accompanies the increase of CBV caused by isoflurane anesthesia in dogs. The current available data do not explain why with isoflurane ICP does not decrease as a result of decreased $R_a$. It may be that CSF volume approaches the limit to its contraction, that isoflurane increases the elastance of brain tissue or the cerebral vascular compartment, or that isoflurane causes a verticle straightening of the $V_a$/ICP slope at decreased ICP so that $V_a$ approaches zero as soon as ICP decreases below normal.

The mechanism(s) by which anesthetics alter $R_a$ are not known. The classical view has been that CSF is absorbed through cranial arachnoid villi into the superior sagittal sinus, and through spinal arachnoid villi located on the dorsal roots projecting into the dural sinuses. It was thought that these villi comprised a series of tubules directly connecting the subarachnoid and dural sinus compartments and that the tubules were kept open when a pressure gradient existed between CSF and dural blood. Under such a system, anesthetics could alter $R_a$ by changing the conductance of the arachnoid villi or the pressure gradients from CSF to blood. However, electron microscopic studies showed that the villus is covered with a continuous cellular membrane interspersed between the CSF and blood. Identification of giant vacuoles and transcellular channels in the cellular membrane has led some investigators to propose that these pores are the route for bulk flow and transport of CSF into blood. If so, anesthetics may alter $R_a$ by inhibiting or facilitating formation of vacuoles or temporary transcellular channels, or by altering the pressure gradient across the mesothelial cell membrane. Another view is that a significant fraction of CSF does not flow into dural blood but rather crosses the arachnoid-dura barrier at the root exit zones of cranial and spinal nerves to enter “prelymphatic” tissue spaces. Anesthetics may alter $R_a$ via this route by changing the conductance at the root exit zones or the pressure gradient from CSF to either the prelymphatic space or the defined lymphatic system.

Both during enflurane anesthesia and isoflurane anesthesia, $V_a$ increased directly as CSF pressure was increased. The direct relationship between $V_a$ and CSF pressure observed here was similar to that previously reported in dogs, rabbits, and goats. During isoflurane anesthesia, $V_a$ did not change significantly as CSF pressure was increased. This observation is consistent with previous reports that $V_f$ remains constant over a wide range of CSF pressures. The tendency for $V_f$ values to fall (NS) at increased CSF pressure during enflurane anesthesia likely does...
not represent a departure from the usual $V_r$/CSF pressure relationship but rather the effect of time on enflurane-stimulated $V_r$. Artru et al. previously reported that during enflurane anesthesia, $V_r$ decreased by $\sim 7\%$/h after initially increasing by 50%. In the present study, mean $V_r$ values at any increased CSF pressure level reflected a mean time interval of $\sim 1.8$ h after control measurements and were correspondingly lower (16%, NS) compared with control $V_r$. Control $V_r$ during enflurane was 58% greater than $V_r$ during isoflurane anesthesia, which previously was reported to produce no change in $V_r$ from normal values. 

It is not known whether the commonly used potent inhalational anesthetics alter $R_h$ in humans and, if so, whether altered CSF dynamics play a meaningful role in the regulation of ICP. However, because isoflurane decreases $R_h$ in dogs, it may offer an advantage over enflurane or halothane for patients who are at risk for increased ICP and would benefit from improved spatial compensation by CSF volume.

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