Canine Cerebral Oxygen Consumption during Enflurane Anesthesia and Its Modification during Induced Seizures

John D. Michenfelder, M.D.,* and Roy F. Cucchiara, M.D.†

The effects of enflurane at <0.1, 2.2, and 4.2 per cent (end-expired) concentrations on cerebral metabolism and circulation were studied in six dogs. A 34 per cent decrease in cerebral oxygen consumption (CMRO₂) occurred at 2.2 per cent (approximately MAC), and no further decrease was observed at 4.2 per cent. Cerebral blood flow (CBF) was increased at each of the higher concentrations despite progressive significant decreases in arterial pressure. In four additional dogs, anesthesia was maintained at 1.5 MAC enflurane (3.4 per cent end-expired) and seizures were induced by hyperventilation (PaCO₂ 20 mm Hg) and intermittent hand clapping. Typical electroencephalographic (EEG) seizure patterns were accompanied by a 48 per cent increase in CMRO₂ (mean) and gross skeletal muscle activity. Control conditions were re-established and seizures were again induced by pentylentetrazol (30 mg/kg). These seizures could not be differentiated from those previously induced by hypocapnia and hand clapping. We conclude that enflurane generally resembles other halogenated anesthetics in its effects on CMRO₂ and CBF but differs in producing seizures similar to those produced by a known convulsant. (Key words: Anesthetics, volatile: enflurane; Brain: metabolism: enflurane; Brain: blood flow: enflurane; Metabolism: brain: enflurane.)

The CEREBRAL METABOLIC and functional effects of enflurane (Ethane)† are of particular interest because of the occasional clinical observation that its administration may be associated with the onset of spontaneous skeletal muscle activity. This activity has been variously viewed as a minor nuisance that is easily controlled with muscle relaxants, as a useful sign of excessive anesthetic depth, and as the possible manifestation of seizure activity. In dogs, such muscle activity can be produced consistently and is accompanied by the appearance of a seizure pattern in the EEG.† In man, spontaneous† EEG seizure patterns accompanied by an apparent increase in cerebral oxygen consumption have been reported† to occur in some volunteers exposed to moderately deep levels of enflurane anesthesia. Cerebral functional disturbances following enflurane anesthesia have not been reported.

The present study was designed to determine the effects of enflurane on canine cerebral metabolism and blood flow, in both the presence and the absence of circumstances associated with spontaneous skeletal muscle activity and EEG seizure patterns. The effects observed during periods of spontaneous skeletal muscle activity were then compared with those produced by the administration of pentylentetrazol, a known convulsant.

Methods

Ten unmedicated, fasted mongrel dogs (weights, 14–20 kg) were anesthetized with enflurane (2.5–3.0 per cent, inspired) in N₂ and O₂. Succinylcholine (20 mg) was given to facilitate endotracheal intubation and thereafter was continued (rate, 150 mg/hr) to maintain muscle paralysis. Ventilation was controlled with a Harvard pump incorporated.

* Associate Professor of Anesthesiology, Mayo Graduate School of Medicine (University of Minnesota), Rochester.
† Consultant in Anesthesiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.
Received from the Department of Anesthesiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901. Supported in part by Research Grants NS-7507 and HL-4881 from the National Institutes of Health, Public Health Service, and by Ohio Medical Products, a Division of Airco, Inc.
Address reprint requests to Dr. Michenfelder.

† Trademark of Ohio Medical Products, a division of Airco, Inc.
in a nonbreathing system. Cannulas were inserted in a femoral artery for pressure recording (strain gauge) and blood sampling and in a femoral vein for reinfusion of blood and drug administration. Each dog was then positioned prone and a subarachnoid catheter was placed through a Tuohy needle inserted at the level of the lumbar sacral interspace. Cerebrospinal fluid pressure (CSFP) was transduced by a strain gauge, the occiput being used as the zero reference level.

Cerebral blood flow (CBF) was measured directly, as previously described, the blood flow measured was almost exclusively that from the cerebral hemispheres. Blood oxygen contents were calculated from measurements of oxyhemoglobin concentrations (IL-128 CO-Oximeter) and O₂ tensions (IL electrodes, 37°C). Blood glucose contents were determined by an enzymatic technique. Cerebral metabolic rates for oxygen (CMRO₂) and glucose (CMRglucose) were calculated as the product of CBF and the respective arterial-sagittal sinus blood-content differences [Cva-Cv]. Oxygen–glucose index (OGI) was calculated as suggested by Cohen et al. Cerebral vascular resistance (CVR) was calculated as the ratio of mean arterial pressure (MAP) and CBF.

During the surgical preparation, the following standard conditions were established: Fio₂, 125 ± 8 mm Hg (mean ± SE); Paco₂, 40 ± 2 mm Hg; pH, 7.39 ± 0.02; brain temperature (parietal epidural thermistor), 37.1 ± 0.1°C. In all dogs, hemoglobin concentrations were greater than 11 g/100 ml, MAP's exceeded 70 mm Hg, and the EEG was continuously displayed (oscilloscope) and intermittently recorded from bifrontal electrodes.

The effects of enflurane (end-expired concentrations: 0.1, 2.2, and 4.2 per cent) on CBF, CMRO₂, CMRglucose, OGI, CVR, CSFP, and the EEG were examined in six dogs. The sequence of the concentrations studied was varied in each dog. For CBF and CMRO₂ values at each concentration of enflurane were determined from eight to ten sequential CBF measurements (at 2-3-minute intervals) with simultaneous blood sampling for determination of Cva-Cv. CMRglucose values were calculated from two to three measurements of CBF with simultaneous sampling for Cva-Cv; sampling was limited to periods of steady CBF, and glucose values were discarded when large fluctuations in the arterial concentration occurred.

The responses of CBF to Paco₂, in these same six dogs were determined when the end-expired concentration of enflurane was 2.2 per cent. For this purpose, the animals were hyperventilated at a constant minute volume and Paco₂ was altered by varying inspired CO₂. CBF was determined, in duplicate, at each of three Paco₂ tensions (30 ± 1; 42 ± 1; 53 ± 1 mm Hg), with appropriate variation in the sequence of study so as to include all possibilities.

In four additional dogs, the same standard conditions were established except for an end-expired enflurane concentration of 3.4 per cent and the absence of succinylcholine infusion. After CMRO₂ had been determined, EEG recorded, and skeletal muscle activity...
TABLE 1. Cerebral Metabolic and Vascular Effects of Enflurane

<table>
<thead>
<tr>
<th>Function</th>
<th>&lt;0.1</th>
<th>2.2</th>
<th>4.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMR&lt;sub&gt;O&lt;/sub&gt;, ml/100 g/min</td>
<td>5.54</td>
<td>3.64*</td>
<td>3.69*</td>
</tr>
<tr>
<td>CMR&lt;sub&gt;glucose&lt;/sub&gt;, mg/100 g/min</td>
<td>7.09</td>
<td>5.33</td>
<td>5.23</td>
</tr>
<tr>
<td>OGI</td>
<td>1.06</td>
<td>0.93</td>
<td>0.93</td>
</tr>
<tr>
<td>CBF, ml/100 g/min</td>
<td>70</td>
<td>77</td>
<td>93*</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>144</td>
<td>95*</td>
<td>76*</td>
</tr>
<tr>
<td>CVR, mm Hg/ml/100 g/min</td>
<td>2.19</td>
<td>1.37</td>
<td>0.83*</td>
</tr>
<tr>
<td>CSFP, mm Hg</td>
<td>7</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

*Significantly different from <0.1% value (P < 0.05).

observed, the animals were hyperventilated (P<sub>CO</sub>2, 20 ± 1 mm Hg). CMR<sub>O</sub> was determined, the EEG was recorded, and changes in skeletal muscle activity were noted. Then, over a period of 3 to 4 minutes, repetitive loud hand clapping was carried out with simultaneous determinations of CBF and CMR<sub>O</sub> at frequent intervals (every 30 to 60 seconds), continuous recording of the EEG, and observation of muscle activity. The animals were then returned to the normocapnic state and baseline determinations were repeated. Thereafter, pentylenetetrazol (30 mg/kg, iv) was administered and a final set of frequent CBF and CMR<sub>O</sub> determinations was obtained, together with a continuous EEG recording. The existence of statistically significant differences (P < 0.05) between group means was identified by analysis of variance. Individual group means were compared by critical difference testing and by Student's t test for paired data. A regression equation describing CBF response to CO<sub>2</sub> was calculated by the method of least squares.

Results

**CMR<sub>O</sub> and CMR<sub>glucose**

Enflurane in concentrations approximating the minimum alveolar concentration (MAC, 2.2 per cent) caused a significant decrease (34 per cent) in mean CMR<sub>O</sub>, compared with CMR<sub>O</sub> at expired concentrations of less than 0.1 per cent (fig. 1, table 1). Further increases in enflurane concentrations to near 2.0 MAC (4.2 per cent) caused no further decrease in CMR<sub>O</sub>. These changes were accompanied by comparable decreases in CMR<sub>glucose</sub>; accordingly, OGI remained near unity.

**CBF**

Progressive increases in mean CBF accompanied increases in the concentrations of enflurane in five of six dogs despite progressive, significant decreases in MAP in all dogs. The increase in CBF was significant at 4.2 per cent enflurane and was totally accounted for by a significant decrease in CVR. The changes in CBF were not sufficient to alter CSFP. The response of CBF to change in P<sub>CO</sub>2 at 2.2 per cent enflurane was comparable to that previously observed with other halogenated volatile anesthetics<sup>4,8</sup> (Cucchiara et al., unpublished data) (fig. 2). These changes were totally accounted for by changes in CVR and were not sufficient to alter CSFP significantly (although mean CSFP increased from 6 ± 2 to 10 ± 3 mm Hg at the lowest and highest P<sub>CO</sub>2 levels, respectively).

**EEG**

With increases in enflurane concentration, the EEG changed progressively from a high-
frequency, low-amplitude pattern at less than 0.1 per cent through a low-frequency, high-amplitude pattern at 2.2 per cent to a pattern of bursts of spikes followed by electrical silence at 4.2 per cent. These patterns are similar to those previously found in both man⁹-¹⁰ and the cat.¹¹

HYPOCAPNIA AND HAND CLAPPING

The combined stimuli of hypocapnia ($\text{Paco}_2$, 20 mm Hg) and repetitive hand clapping produced, at 1.5 MAC enflurane (3.4 per cent), abrupt precipitous increases in $\text{CMR}_{\text{O}_2}$ (table 2) and CBF, both of which were accompanied by the simultaneous appearance of a seizure pattern in the EEG (fig. 3). During this period the mean peak increase in $\text{CMR}_{\text{O}_2}$ was 48 per cent; it was short-lived despite continuation of both stimuli. The increase in CBF was of a similar magnitude, was not associated with change in MAP, and was also of brief duration. Some spontaneous skeletal muscle activity (nonthyrmic, jerking movements) was observed at the start of hypocapnia and became marked (at times clonic) during the period of hand clapping. When normocapnia was re-established, baseline responses ($\text{CMR}_{\text{O}_2}$, EEG, and muscle activity) were again observed. A single dose of pentylentetrazol (30 mg/kg, iv) immediately reproduced all of the changes previously produced by hypocapnia and hand clapping. The only consistent difference following pentylentetrazol was prolongation of the changes in EEG, muscle activity, and $\text{CMR}_{\text{O}_2}$.

Discussion

In the presence of standard conditions (normothermia, normocapnia, normal $\text{pH}$, and normal oxygen delivery), the effects of enflurane on canine CBF and $\text{CMR}_{\text{O}_2}$ resemble those previously observed in response to other halogenated volatile anesthetics (halothane, methoxyflurane, and isoflurane [Cucchiara et al., unpublished data]). All of these anesthetics produce decreases in both $\text{CMR}_{\text{O}_2}$ and CVR and hence consistent increases in the ratio of CBF to $\text{CMR}_{\text{O}_2}$. Between these anesthetics there are individual quantitative differences, differences in dose response, and differences in EEG patterns at equipotent concentrations (up to 2.0 MAC). Both halothane and enflurane produce maximal changes in $\text{CMR}_{\text{O}_2}$ at 1.0 MAC and little further change at 2.0 MAC, whereas methoxyflurane and isoflurane are accompanied by progressive decreases in $\text{CMR}_{\text{O}_2}$ as concentrations are increased to 2.0 MAC. CBF changes are quantitatively least with methoxyflurane, whereas halothane and isoflurane produce the greatest increases in CBF. With all four anesthetics, the responses of CBF to change in $\text{Paco}_2$ at 1.0 MAC are virtually identical.

Clinically, differences among these anesthetics have been observed. Enflurane differs strikingly in its capacity to cause spontaneous skeletal muscle activity accompanied by seizure-like patterns in the EEG. These changes have been most commonly observed when deep anesthesia and hypocapnia exist together. In the dog, spontaneous muscle activity accompanied by the abrupt appearance of a seizure pattern in the EEG has been consistently produced at 1.5 MAC enflurane by the combined stimuli of hypocapnia ($\text{Paco}_2$, 20–30 mm Hg) and repetitive
Table 2. Responses of $\text{CMR}_{\text{o}}$ (ml/100 g/min) to Hypocapnia, Hand Clapping, and Pentylentetrazol during Anesthesia with Enflurane (3.4 Per Cent, End-expired)

<table>
<thead>
<tr>
<th></th>
<th>Initial Normocapnia</th>
<th>Hypocapnia</th>
<th>Hypocapnia, Clapping</th>
<th>Final Normocapnia</th>
<th>Normocapnia, Pentylentetrazol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog 7</td>
<td>3.97</td>
<td>4.17</td>
<td>5.57</td>
<td>3.57</td>
<td>4.32</td>
</tr>
<tr>
<td>Dog 8</td>
<td>2.72</td>
<td>2.93</td>
<td>4.13</td>
<td>2.27</td>
<td>3.20</td>
</tr>
<tr>
<td>Dog 9</td>
<td>2.95</td>
<td>3.48</td>
<td>5.66</td>
<td>3.00</td>
<td>5.90</td>
</tr>
<tr>
<td>Dog 10</td>
<td>2.97</td>
<td>2.99</td>
<td>4.16</td>
<td>2.69</td>
<td>3.25</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>3.15 ± 0.28</td>
<td>3.39 ± 0.29</td>
<td>4.96* ± 0.47</td>
<td>2.88 ± 0.27</td>
<td>4.17* ± 0.63</td>
</tr>
</tbody>
</table>

* Significantly different from preceding normocapnic value ($P < 0.05$).

hand clapping. In volunteers, Wollman and associates observed, at enflurane concentrations approximating 2.0 MAC, a 50 per cent decrease in $\text{CMR}_{\text{o}}$; in three of the six subjects studied at this concentration, however, seizure patterns spontaneously developed, together with an immediate increase in differences of arterial–jugular bulb blood-oxygen content. In the present study, the observed effects of an established convulsant dose of pentylentetrazol on canine $\text{CMR}_{\text{o}}$, EEG, and skeletal muscle activity did not significantly differ from those produced by the combina-

![Fig. 3. Responses of $\text{CMR}_{\text{o}}$, skeletal muscle activity, and EEG to seizures produced by both enflurane and pentylentetrazol in a single dog. EEG strips were taken at times indicated by the broken lines. At baseline conditions of normocapnia and 1.5 MAC enflurane (Panel A), $\text{CMR}_{\text{o}}$ was steady, EEG showed intermittent spiking activity, and there was no skeletal muscle activity. When hypocapnia was induced (Panel B), there was a modest increase in $\text{CMR}_{\text{o}}$ and slight spontaneous muscle activity with no change in the EEG. With hand clapping, a burst of EEG activity was accompanied by marked muscle activity and an abrupt increase in $\text{CMR}_{\text{o}}$. With return to normocapnia (Panel C), $\text{CMR}_{\text{o}}$, EEG, and muscle activity returned to baseline conditions and one dose of pentylentetrazol reproduced all of the changes previously observed with hypocapnia and hand clapping.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931541/)
tion of 1.5 MAC enflurane, hypoxia, and repetitive hand clapping. By these standards, enflurane must be viewed as a potential true convulsant in the dog. Accordingly, in man the occurrence of spontaneous skeletal muscle activity during enflurane anesthesia should be viewed as a probable manifestation of a seizure. There is no evidence, however, either in the present study or in the study by Wollman and associates, that cerebral oxygenation is threatened during the period of seizure activity. Furthermore, in Wollman and associates' volunteers, cerebral function was not apparently disturbed in the post-anesthetic period. Nonetheless, it is reasonable to view seizure activity as an undesirable side effect of any anesthetic technique. The occurrence of seizures during enflurane anesthesia presumably can be minimized by avoiding hypoxia and enflurane concentrations exceeding 1.5 MAC. These considerations are relative contraindications to the use of moderate or deep levels of enflurane in such procedures as craniotomy, in which induced hypoxia is of itself a recognized beneficial technique and in which the maintenance of normocapnia would likely result in an increase in intracranial pressure secondary to an increase in CBF.

References


