Brain Surface Protrusion during Enflurane, Halothane, and Isoflurane Anesthesia in Cats

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Steven M. Toutant, M.D.,‡ Harvey M. Shapiro, M.D.§

Using a noncontact displacement transducer, the authors measured protrusion of the feline cortical surface through a standardized craniotomy during acute equi-MAC exposures to enflurane, halothane, and isoflurane. Each agent was studied at 0.5, 1.0, and 1.5 MAC concentrations (plus 75% N₂O) without support of blood pressure. A repeat 1.0 MAC exposure was made, during which angiotensin was infused to maintain mean arterial pressure (BP) at approximately 145 mmHg. Normocapnia was maintained during all studies. In the absence of BP support, halothane produced significantly greater protrusion of the brain surface than did equi-MAC concentrations of isoflurane at all levels and greater protrusion than enflurane at 1.0 and 1.5 MAC. Halothane-induced protrusion exceeded that seen during isoflurane administration by a factor of 2.5 at 0.5 MAC (P < 0.05); by 1.7 at 1.0 MAC (P < 0.01); and by 2.2 at 1.5 MAC (P < 0.001) and exceeded that seen during enflurane administration by a factor of 1.6 at 1.0 MAC (P < 0.01) and 2.2 at 1.5 MAC (P < 0.001). When anesthetic-induced differences in BP were eliminated by arterial pressure support, the disparity between the protrusion caused by halothane as compared with that caused by enflurane and isoflurane (1.0 MAC) was exaggerated. At similar BP (during 1.0 MAC exposure), halothane produced approximately 2.4 times as much protrusion as both enflurane and isoflurane (P < 0.0001).

The results indicate that enflurane (1.0 and 1.5 MAC) and isoflurane (all levels) cause markedly less protrusion of the brain into a craniotomy than does halothane. The findings roughly parallel the known effects of these agents on cerebral blood flow and probably reflect differences in anesthetic-induced changes in cerebral blood volume. If applicable to human anesthesia, they suggest that in situations during intracranial surgery where administration of a volatile anesthetic is deemed preferable to the use of an additional fixed agent, that isoflurane may be the volatile agent of choice. (Key words: Anesthesia, neurosurgical. Anesthetics, volatile: enflurane; halothane; isoflurane. Brain: blood flow; autoregulation; blood volume.)

THE VOLATILE ANESTHETIC AGENTS are known to be cerebral vasodilators and, as a consequence, their role in neuroanesthesia has been limited. Agents that dilate the cerebral vasculature can cause increases in cerebral blood flow (CBF) and hence cerebral blood volume. The latter will result in a compliance-dependent increase in intracranial pressure (ICP) when the cranium is closed or bulging of the brain into the surgical field during craniotomy. The available CBF information suggests that the magnitude of this effect should be different with enflurane, halothane, and isoflurane, but the data are incomplete.12-4

This laboratory has recently developed a noncontact method for measuring movement of the cortical surface.5 We employed this technique to perform a comparison of the brain volume effects of the three commonly available volatile anesthetics in cats. Our results are consistent with recent suggestions that isoflurane may be more suitable for use in neurosurgery than previously available agents.6,7

Methods

Eighteen mongrel cats of either sex (weight 2.9–4.0 kg) were studied. Anesthesia was induced in a plexiglass box by administration of 4% halothane. The animals were paralyzed with pancuronium (0.5 mg/kg), intubated and ventilated (tidal volume = 15 ml/kg; rate = 15 breaths/min) with an inspired mixture of 1–1.25% halothane in 75% N₂O with oxygen. Carbon dioxide was added to the inspired mixture to maintain normocapnia (PaCO₂ 29–31 mmHg). Relaxation was maintained with increments of pancuronium (ca. 0.5 mg/h), and maintenance fluids (normal saline) were administered at 5 ml·kg⁻¹·h⁻¹. Oesophageal temperature was servo-controlled (heat lamp) at 37°C. Arterial and central venous catheters were inserted via femoral vessels. The animal was turned into a sphinx position, and the head was secured in a stereotactic frame with the ear bars 12 cm above the table surface. An extensive, standardized, right fronto-parietal craniotomy was performed using a high speed burr and small rongeurs. The anterior margin followed the coronal suture, and the medial margin was 5–6 mm from the midline. The craniotomy extended laterally to the point at which the skull surface became vertical and caudally to the parietal

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emminence. The dura was excised, and drying of the brain surface was prevented by continuous saline irrigation. Brain surface movement was measured with a noncontact displacement-measuring device. The device, which was mounted on the stereotactic frame and positioned over the craniotomy, provided a continuous measurement of the distance between itself and an aluminum foil target placed on the brain surface. The metal target results in eddy currents in an electromagnetic field generated by the sensor. The eddy currents cause an impedance variation, which is proportional to the distance between sensor and target. The instrument will resolve distance variations of $\geq 6.0 \times 10^{-5}$ mm where the rise time of the transient is greater than 10 μs. Blood pressure, central venous pressure (CVP), expired CO$_2$, expired inhalation agent concentration (sampled at the tip of the endotracheal tube, Beckman LB-2), and brain surface position were recorded continuously. EKG and EEG (brass screws anterior and posterior to the craniotomy) were monitored continuously and recorded intermittently.

At the conclusion of the surgical preparation, wound margins were infiltrated with 0.25% bupivacaine, and the halothane was discontinued. Administration of 75% N$_2$O continued throughout the experiment. Noise and contact with the animal were avoided. A 90-min halothane "washout" period ensued, and end-tidal halothane concentration was <0.05% for at least 20 min before subsequent study. A single agent, chosen randomly, was studied in each animal (six each for enflurane, halothane, and isoflurane). Each study consisted of four exposures to the selected agent. Exposures were made at the 0.5, 1.0, and 1.5 MAC levels (plus 75% N$_2$O).†† The sequence for these three exposures was varied systematically such that each of the six possible sequences was studied. The fourth and final exposure in each animal was a repeat 1.0 MAC administration, during which angiotensin II was infused to maintain mean arterial pressure above 130 mmHg. Each exposure was of 5-min duration (see "Discussion"). Inspired concentration was adjusted such that end-tidal inhalation agent concentration reached but did not exceed the chosen MAC multiple (+/− 0.05%) within 2 min. In preliminary experiments, it was observed that P$_{ACO_2}$ fell during inhalation agent exposures. Accordingly, carbon dioxide was added to the inspired gas to maintain end-tidal CO$_2$ concentration at the control level. Arterial blood gases (pH, P$_{ACO_2}$, P$_{O_2}$) and physiologic variables recorded immediately before each exposure were used as control values. Blood gas analysis was repeated at the end of the 5-min exposure, and changes in brain surface position and physiologic variables were noted. A 45-min interval between exposures assured an end-tidal inhalation agent concentration of <0.05% prior to repeat study. The data were analyzed using repeated measures analysis of variance. Pair-wise comparison of means used pooled standard errors based on the analysis of variance. P < 0.05 was considered significant.

** Results **

The weight, blood pressure, P$_{ACO_2}$, and brain protrusion data are presented in table 1. The mean weights

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** Table 1. P$_{ECO_2}$ (mmHg) and Mean Arterial Pressure (BP) (mmHg) Prior to Exposures (t = 0); and P$_{ECO_2}$, BP, and Brain Protrusion (mm) at the Conclusion (t = 5 min) of Exposures to Enflurane, Halothane, and Isoflurane at 0.5, 1.0, and 1.5 MAC and 1.0 MAC with Angiotensin Support of Arterial Pressure (100/5 Angiotensin) (The weights (±SD) for each group appear in parentheses beside the respective agents.)

<table>
<thead>
<tr>
<th>MAC Level</th>
<th>t = 0</th>
<th>t = 5 min</th>
<th>t = 5 min</th>
<th>t = 5 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P$_{ECO_2}$ ± SE</td>
<td>BP ± SE</td>
<td>P$_{ECO_2}$ ± SE</td>
<td>BP ± SE</td>
</tr>
<tr>
<td>Enflurane (3.39 ± 0.48 kg)</td>
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<td></td>
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<tr>
<td>0.5</td>
<td>29.7 ± 0.6</td>
<td>157 ± 7</td>
<td>29.5 ± 0.6</td>
<td>108 ± 8</td>
</tr>
<tr>
<td>1.0</td>
<td>30.2 ± 0.8</td>
<td>159 ± 4</td>
<td>30.0 ± 0.5</td>
<td>72 ± 10.4</td>
</tr>
<tr>
<td>1.5</td>
<td>29.8 ± 0.6</td>
<td>160 ± 5</td>
<td>29.8 ± 0.9</td>
<td>52 ± 10.1</td>
</tr>
<tr>
<td>1.0/angiotension</td>
<td>29.5 ± 0.6</td>
<td>161 ± 7</td>
<td>30.0 ± 0.8</td>
<td>151 ± 6</td>
</tr>
<tr>
<td>Halothane (3.15 ± 0.25 kg)</td>
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</tr>
<tr>
<td>0.5</td>
<td>30.7 ± 0.3</td>
<td>155 ± 7</td>
<td>28.8 ± 0.7</td>
<td>119 ± 5</td>
</tr>
<tr>
<td>1.0</td>
<td>30.8 ± 0.6</td>
<td>149 ± 6</td>
<td>30.2 ± 0.8</td>
<td>90 ± 8</td>
</tr>
<tr>
<td>1.5</td>
<td>30.5 ± 0.6</td>
<td>145 ± 4</td>
<td>29.0 ± 0.4</td>
<td>63 ± 6</td>
</tr>
<tr>
<td>1.0/angiotension</td>
<td>30.7 ± 0.6</td>
<td>158 ± 6</td>
<td>31.3 ± 0.6</td>
<td>141 ± 6</td>
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<tr>
<td>Isoflurane (3.32 ± 0.33 kg)</td>
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</tr>
<tr>
<td>0.5</td>
<td>30.7 ± 0.3</td>
<td>151 ± 7</td>
<td>30.2 ± 0.8</td>
<td>120 ± 10</td>
</tr>
<tr>
<td>1.0</td>
<td>30.5 ± 0.6</td>
<td>143 ± 6</td>
<td>31.0 ± 0.5</td>
<td>108 ± 4</td>
</tr>
<tr>
<td>1.5</td>
<td>30.3 ± 0.3</td>
<td>146 ± 5</td>
<td>30.5 ± 0.8</td>
<td>95 ± 9</td>
</tr>
<tr>
<td>1.0/angiotension</td>
<td>30.0 ± 0.6</td>
<td>149 ± 9</td>
<td>30.8 ± 1.0</td>
<td>148 ± 7</td>
</tr>
</tbody>
</table>

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** ** KD-2310-6U, Kaman Sciences Corp., Colorado Springs, Colorado.

†† Minimum alveolar concentration (MAC) values were determined in a separate group of eight conditioned cats according to the method of Eger et al. The values were enflurane, 2.37 ± 0.06% (SEM), halothane, 1.19 ± 0.05%, and isoflurane, 1.61 ± 0.04%.
for the three groups were not significantly different. There were no significant differences within or between groups in terms of the PaCO₂ levels prior to and at the conclusion of any MAC level exposure.

The protrusion data for the 0.5, 1.0 (BP unsupported), and 1.5 MAC levels also are presented graphically in figure 1. At the 0.5 MAC level, halothane produced 2.5 times as much protrusion as isoflurane (i.e., 0.40 ± 0.09 mm vs. 0.16 ± 0.02 mm) (P < 0.05). The protrusion observed during enflurane administration was intermediate and was not significantly different from that observed during exposure to either halothane or isoflurane. At the 1.0 MAC level, halothane produced 1.74 times as much brain surface protrusion as isoflurane (P < 0.01) and 1.64 times that seen during enflurane administration (P < 0.01). At the 1.5 MAC level, the protrusion that occurred during halothane administration was 2.2 times that seen with either enflurane or isoflurane (P < 0.0001).

A comparison of the protrusion observed with and without blood pressure support at the 1.0 MAC level is presented in figure 2. Angiotensin blood pressure support resulted in significantly greater protrusion (as compared with 1.0 MAC unsupported) for enflurane (P < 0.05) and halothane (P < 0.001). The apparent increase during isoflurane administration was not significant (probably because protrusion decreased 0.02 mm during BP support in one animal). Pair-wise comparisons of the protrusion increments revealed that the increment was greater during administration of halothane than either enflurane (P < 0.0001) or isoflurane (P < 0.0001). The enflurane and isoflurane protrusion increments were not statistically different. The mean blood pressures during support were similar (enflurane 151 ± 6 (SEM) mmHg; halothane 141 ± 6 mmHg; isoflurane 148 ± 7 mmHg), and at these pressures halothane produced approximately 2.4 times as much protrusion as either enflurane or isoflurane (P < 0.0001) (i.e., 1.75 ± .14 mm vs. 0.73 ± .10 mm and 0.72 ± .12 mm).

![Graph](image)

**Fig. 1.** Brain surface protrusion during administration of enflurane (E), halothane (H), and isoflurane (I) at 0.5, 1.0, and 1.5 MAC concentrations (plus 75% N₂O). *H vs. I, P < .05; **H vs. E and I, P < .01; ***H vs. E and I, P < .0001.

![Graph](image)

**Fig. 2.** Brain surface protrusion during administration of 1.0 MAC enflurane, halothane, and isoflurane (plus 75% N₂O) with and without angiotensin support of mean arterial pressure (BP). Mean pressures during the support phase were not significantly different. *The protrusion difference (supported vs. unsupported) was greater for halothane than enflurane or isoflurane (P < .0001). The enflurane and isoflurane differentials were not significantly different.
mm). Note that during 1.0 MAC administration without pressure support, mean arterial pressures were lowest during enflurane administration and greatest during isoflurane administration. (Table 1) As a consequence, the pressure increment during the support phase was greatest for enflurane and least for isoflurane.

Discussion

During a craniotomy, the administration of drugs that increase CBF, and hence the volume of the intracranial contents, will cause a shift of the brain toward the surgical field. The result may be a more difficult surgical exposure with a greater risk of retractor-related ischemia or mechanical damage. With larger movements, mechanical injury to the brain may result from herniation between intracranial compartments or through the craniotomy. Our study examined the extent to which acute exposures to enflurane, halothane, and isoflurane in the presence of normocapnia caused a protrusion of a normal brain into a craniotomy. The results indicate that halothane produces markedly more protrusion than either enflurane (1.0 and 1.5 MAC) or isoflurane (0.5, 1.0, and 1.5 MAC). There were no statistically significant differences between the effects of enflurane and isoflurane, although at the 0.5 MAC level, the results suggest an advantage for isoflurane.

Our use of brain surface movement in the comparison of the cerebrovascular effects of anesthetic agents is novel. Brain protrusion has obvious clinical relevance, but, in addition, the method offered certain physiologic advantages over more traditional ICP and CBF measurement techniques. A craniotomy, such as we employed, produces a situation of theoretically infinite compliance (unless the expanding brain seals the perimeter of the field) and eliminates the influence that inter- and intra-individual differences in compliance would have on ICP measurements in a closed-cranium preparation. We were concerned in particular that multiple exposures in a single animal, with recurrent elevation of ICP, would result in cerebrospinal fluid (CSF) shifts (to the spinal space). Such shifts would have the effect of altering preexposure compliance, thereby making meaningful comparisons of ICP changes difficult. We feel that our open-cranium method obviates this difficulty. As confirmation, we observed both in this study and in preliminary studies that the brain surface consistently returned to the preexposure position whenever exposures were brief. CBF measurement during circumstances similar to those we describe should provide valid comparisons; however, brain surface movement measurement allows “on-line” assessment and gives evidence of a steady state at the time selected for comparison. No accurate on-line method is available for CBF measurements in cats.

It is probable that the changes in brain surface protrusion that we observed were the result of alterations in cerebral blood flow acting via the effect of CBF on cerebral blood volume. We cannot exclude the interplay of effects of the inhalation agents on CSF dynamics (rate of production, outflow resistance), on tissue volume, or specific effects on cerebral venous tone. However, while there is evidence that inhalation agents can alter CSF dynamics, important influence in this study is probably precluded by the time course of exposure (i.e., too brief). We did not measure brain tissue specific gravity or water content and therefore cannot exclude a change in tissue volume. However, the rapidity of the changes that were observed would argue for a vascular rather than a tissue compartment alteration. With respect to venous tone, we know of no evidence to suggest (or refute) a specific effect of volatile agents on cerebral venous tone. Changes in extracranial venous pressure also might alter cerebral venous volume. However, increased CVP was not observed during inhalation agent exposure and therefore was not a contributing effect.

Our study employed a rapid elevation of end-tidal concentration and a short period of exposure. This method may have exaggerated the changes that occurred by minimizing the time available for compensatory mechanisms. However, we felt that a short exposure was desirable for two reasons. First, we sought to minimize the impact of influences other than CBF-related changes in CBV. In our preliminary studies, we observed that the initial brain surface protrusion plateaus were not sustained beyond 5–10 min and that upon discontinuation of the agent in these situations, the brain subsided to levels below control position. Accordingly, it was inferred that some uncontrolled variable other than CBF variation (e.g., translocation of CSF into the spinal space, loss of CSF into the craniotomy, changes in CSF dynamics) was influencing brain surface position during prolonged exposure. And second, the short course of each exposure precluded significant saturation of body fat and allowed for a rapid return to end-tidal concentration less than 0.05%. This permitted the completion of four exposures within a relatively short (2.5 h) period of study and thereby minimized the opportunity for deterioration of the preparation. If the short course were to introduce an inaccuracy, it would most probably result from relatively incomplete saturation with the most soluble agent (halothane). If this were a factor, the differences between halothane and the other two agents might have been even greater than those observed. In fact, the 5-min exposure was selected after preliminary studies revealed that it was consistently sufficient to provide a brain surface protrusion plateau and we doubt the interplay of any error related to the short duration of exposure.
While we are convinced that our results are an accurate indication of the impact of acute exposures to enfurane, halothane, and isoflurane in the presence of normocapnia, they do not necessarily apply to either situations of more prolonged exposure or to exposure during hypcapnia. The cerebrovascular effects of the volatile agents may vary with time. In separate studies of the cerebrospinal fluid pressure (CSFP) response to administration of halothane and isoflurane, Adams and two groups of co-workers noted that CSFP elevations subsided overtime in the face of constant inspired concentrations and \( P_{\text{aco}_2} \). Alterations of other than CBF might have accounted for these changes, however, Kassel (personal communication, manuscript in preparation) has observed marked reduction in CBF (microspheres) during 6-h exposures to constant concentrations of halothane and isoflurane in dogs. Albrecht et al. observed a similar phenomenon during 150 minutes of halothane anesthesia (1.0% inspired) in goats. Thus, it appears likely that CBF diminishes with time during exposure to constant concentrations of halothane and isoflurane. If the cerebral vasodilating effects of volatile agents do diminish with time, slow elevation of inspired concentration markedly might attenuate the brain surface position response to volatile agent administration.

Alterations in carbon dioxide tension similarly might modify the results. The CSFP studies of Adams and his co-workers indicate that the institution of hypcapnia simultaneous with the administration of the volatile agent can prevent pressure increases during isoflurane administration and attenuate (but not prevent) those occurring during inhalation of halothane. Simultaneously instituted hypcapnia (which we did not employ) well might have had the same relative effect on brain protrusion. Prior hyperventilation prevented CSFP increases during administration of both agents in the CSFP studies, and similarly in this study, prior institution of hypcapnia altogether might have prevented protrusion increments to levels higher than prehypocapnia control. However, it is likely that the opposing cerebrovascular effects of hypcapnia and volatile agents are additive and that the increments relative to a post-hypocapnia baseline still would be greater for halothane than for the other two agents. The importance of such increments would depend on the clinical circumstances.

Comparisons of the effects of enfurane, isoflurane, and halothane on cerebral blood flow are available in the literature and, in general, parallel the protrusion differences that we observed. The data consistently indicate that halothane produces greater CBF increases than enfurane or isoflurane; however, the relative impact of the latter two varies with species and concentration.

The blood pressure support phase of our study may provide a limited insight into the impact of these three agents on cerebral blood flow autoregulation. The results suggest that impairment is greater with halothane than with either enfurane or isoflurane. The information concerning autoregulation is only indirect because we did not measure cerebral blood flow. However, it is probable that protrusion increments bear some direct relation to CBF changes via the effect of the latter upon cerebral blood volume. A comparison of the protrusions and blood pressures observed with and without blood pressure support at the 1.0 MAC level (table 1) indicates that the increase in brain surface protrusion associated with a given increment of blood pressure was greater for halothane than for enfurane and isoflurane. While this suggests that impairment of autoregulation is greatest with halothane and least with enfurane, the information is limited and does not permit a general statement about the effect of these agents on autoregulation. It is entirely possible that at certain pressures autoregulation is intact for all three agents, that the upper limits of autoregulation differ, and that at our final pressure of approximately 145 mmHg we have exceeded those limits by different amounts. At a lower supported pressure, the differences might well have been less marked.

The implications of this study with regard to autoregulation are in keeping with what little additional information there is concerning the effects of volatile anesthetics. Murphy et al. (abstract cited previously) examined CBF during administration of 1.1 MAC enfurane and halothane with and without support of arterial pressure. Flow increased during pressure support and the increment was greater during halothane administration. A comparable study of isoflurane was not performed. Morita et al. studied CBF autoregulation in monkeys anesthetized with halothane and 70% \( N_2O \) in oxygen. Their report indicates that during administration of 1% halothane (approximately 1.0 MAC in the monkey), autoregulation was abolished completely above a mean arterial pressure of approximately 90 mmHg. They did not study enfurane or isoflurane. Thus, the available information indicates that halothane can cause major impairment of CBF autoregulation and

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+++ Kassel, NF, Division of Neurosurgery, University of Iowa College of Medicine.
§§ Murphy et al: Abstract cited previously.

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that enflurane has a similar but less pronounced effect. There are no data concerning the effect of isoflurane on autoregulation.

In summary, our results indicate that acute isocapnic administration of enflurane and isoflurane (plus 75% N₂O) in normocapnic cats causes markedly less protrusion of the brain surface into a craniotomy than does halothane. If our results are applicable to human anaesthesia, they suggest that in circumstances during intracranial surgery where introduction of a volatile seems preferrable to the use of additional fixed agent, that isoflurane may be the preferred agent. (Enflurane's epileptogenic properties should probably exclude it.) Isoflurane might be expected to cause less protrusion of the brain into the surgical field than halothane and, accordingly, less difficulty with surgical exposure. The results further suggest that at a mean pressure of 145 mmHg (near what is conventionally viewed as the upper limit of autoregulation), halothane causes a greater impairment of autoregulation than enflurane or isoflurane. Our results were obtained in normal cats and are not necessarily directly applicable to human anaesthesia. However, they do suggest that the strictures applied to the use of halothane may not apply necessarily to isoflurane and that further exploration of the use of isoflurane in neurosurgery is warranted.

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References


