EFFECT OF $\text{Pa}_{\text{CO}_2}$ ON CEREBRAL BLOOD FLOW DISTRIBUTION DURING HALOTHANE COMPARED WITH ISOFLURANE ANAESTHESIA IN THE RAT

W. L. YOUNG, A. I. BARKAI, I. PROHOVNIK, H. NELSON AND M. DURKIN

SUMMARY

In order to examine anaesthetic effects on the distribution of cerebral blood flow (CBF) during normo- and hypocapnia, male adult Sprague-Dawley rats were allocated randomly to four groups in a $2 \times 2$ factorial design, using $\text{Pa}_{\text{CO}_2}$ value and anaesthetic agent as between-group factors. Animals were anaesthetized with either 1.38% isoflurane (inspired) or 1.05% halothane (inspired) and the lungs ventilated mechanically at either normocapnia ($\text{Pa}_{\text{CO}_2} 5.1-5.6 \text{kPa}$) or hypocapnia ($\text{Pa}_{\text{CO}_2} 3.1-3.3 \text{kPa}$) for 1 h. CBF was measured using $^{14}$C-iodoantipyrine autoradiography. Local CBF in selected cortical and subcortical regions of interest and area-weighted mean global CBF were calculated. Data were compared by analysis of variance. Normocapnic (mean (SE)) CBF for halothane ($n = 6$) and isoflurane ($n = 7$) was 120 (8) ml/100 g min$^{-1}$ ($\text{Pa}_{\text{CO}_2} 5.6 (0.49) \text{kPa}$) and 117 (9) ml/100 g min$^{-1}$ ($\text{Pa}_{\text{CO}_2} 5.4 (0.5) \text{kPa}$), respectively. Hypocapnic CBF for halothane ($n = 6$) and isoflurane ($n = 6$) was 82 (7) ml/100 g min$^{-1}$ ($\text{Pa}_{\text{CO}_2} 3.3 (0.12) \text{kPa}$) and 82 (6) ml/100 g min$^{-1}$ ($\text{Pa}_{\text{CO}_2} 3.2 (0.12) \text{kPa}$), respectively. Hypocapnia reduced global CBF for both groups by 30% ($P < 0.001$), but there was no difference between anaesthetic agents ($P > 0.8$). Hypocapnia decreased CBF in all local structures examined. Although subcortical structures had similar CBF at both normocapnia and hypocapnia, CBF in three cortical samples was greater ($P < 0.05$) in both the normocapnic and hypocapnic halothane groups than the corresponding isoflurane groups. The CBF reactivity to changes in $\text{Pa}_{\text{CO}_2}$ was similar for both agents (approximately 2 ml/100 g min$^{-1}$ mm Hg). We conclude that halothane is a selective cortical vasodilator compared with isoflurane, but both agents have similar effects on global CBF and local and global CBF reactivity to changes in $\text{Pa}_{\text{CO}_2}$.

KEY WORDS

Anaesthetics, volatile; halothane, isoflurane; Brain: regional cerebral blood flow; Carbon dioxide: hypocapnia.

Halothane and isoflurane are commonly used anaesthetic agents with different effects on cerebral haemodynamics. In particular, isoflurane produces smaller increases in intracranial pressure (ICP) in neurosurgical patients than halothane, especially in the presence of hypocapnia [1], although it is clear that isoflurane may cause increased ICP in some patients [2]. However, the mechanism of the different effect on ICP is not clear, as halothane and isoflurane produce variable effects on cerebral blood flow, depending on the method of measurement [3]. There is evidence that both agents have a similar effect on total cerebral blood volume [4]. Halothane has been described as being a selective cortical vasodilator relative to isoflurane [3]; however, the effect of $\text{Pa}_{\text{CO}_2}$ on this distribution is not known. This knowledge would be useful and may have implications for the use of induced hypocapnia in focal cerebral ischaemia [5]. This study has examined the influence of $\text{Pa}_{\text{CO}_2}$ on the dis-

W. L. YOUNG, M.D. (Department of Anesthesiology); I. PROHOVNIK, PH.D. (Departments of Psychiatry, Neurology and Radiology); A. I. BARKAI, PH.D., H. NELSON, B.S., M. DURKIN, M.S. (Department of Psychiatry); College of Physicians and Surgeons, Columbia University, New York, NY 10032 U.S.A. Accepted for Publication: April 4, 1991.
distribution of cerebral blood flow (CBF) during halothane compared with isoflurane anaesthesia.

MATERIALS AND METHODS

Male adult Sprague-Dawley rats were allocated randomly to four groups in a 2 x 2 factorial design, using two $P_{a\text{CO}_2}$ values and two anaesthesia groups. Animals were anaesthetized with 1 MAC of either 1.38% isoflurane (inspired) or 1.05% halothane (inspired) and the lungs ventilated mechanically to achieve either normocapnia ($P_{a\text{CO}_2}$ 5.1-5.6 kPa) or hypocapnia ($P_{a\text{CO}_2}$ 3.1-3.3 kPa).

Animals were allowed free access to food and water before all experiments. Anaesthesia was induced in a breathing chamber with the appropriate volatile agent. The trachea was cannulated with PE-240 tubing and ventilation was controlled with a Harvard rodent ventilator (Harvard Instruments, South Natick, MA, U.S.A.) using air and supplementary oxygen. Methyltubocurarine iodide 0.1 mg kg$^{-1}$ was given i.v. to produce neuromuscular block. Cannulae were placed in both femoral arteries and veins. Arterial pressure was recorded continuously on a Grass model 7 polygraph (Grass, Inc., Quincy, MA, U.S.A.). Temperature was maintained at 37°C using a heating lamp and monitored by rectal thermistor. Heparin 50 iu was given i.v.

$P_{a\text{CO}_2}$ was verified by arterial blood-gas measurements. After 1 h of mechanical ventilation, CBF was determined by the $^{14}$C-iodoantipyrine indicator fractionation method [6-8] and autoradiographic densitometric analysis [3, 9]. A bolus of $^{14}$C-iodoantipyrine 20 $\mu$Ci kg$^{-1}$ (New England Nuclear, Boston, MA, U.S.A.) in 0.9% saline 0.3 ml was given i.v., with simultaneous withdrawal of a reference flow sample from a femoral artery catheter using a Harvard Pump (Harvard Instruments, South Natick, MA, U.S.A.) set at a rate of 0.393 ml min$^{-1}$. After 10 s the experiment was terminated by decapitation of the rat and the reference flow arterial catheter was withdrawn simultaneously from the femoral artery. The brain was removed quickly and frozen. Blood obtained from the 10-s withdrawal from the femoral artery for reference flow activity was decolourized. Blood radioactivities were assessed by liquid scintillation counting using a Packard Tricarb counter (Packard Instrument Co., Sterling VA, U.S.A.).

Using a cryostat at -20°C, the frozen brains were cut into 20-μm coronal sections at intervals of 240 μm. Sections for each brain were mounted on glass slides and dried on a hot plate. The slides were exposed to Kodak SB-5 autoradiographic film for 1 week together with $^{14}$C-methylmethacrylate standards (Amersham Inc., Arlington Heights, IL, U.S.A.). A digital densitometer (RAS 1000 Research Analysis System, Amersham, Inc.) was used to produce optical density images. Using tissue optical densities, the carbon-14 standards and the reference blood flow radioactivity data, CBF was calculated as described previously [7-9]. "Global CBF" was calculated using a modification of the method described by Hansen and colleagues [3] using area-weighted averages of CBF from six cut sections distributed equally along the rostral-caudal axis of the brain at the level of frontal cortex, caudoputamen, thalamus, substantia nigra, inferior colliculus and cerebellum. (The six section levels correspond to co-ordinates taken from the figure by Paxinos and Watson [10]—bottom of figure 50, lateral 2.9-mm sagittal section of rat brain: -2, 1, 3.5, 6, 9.5 and 11.5.) Local CBF was calculated in selected cortical and subcortical regions of interest.

CBF values for all groups were compared by three-way multivariate analysis of variance (ANOVA) using anaesthetic (halothane vs isoflurane) and ventilation (normocapnia vs hypocapnia) as between-group factors and brain region as a repeated measure. Significance levels were adjusted by the Huynh-Feldt sphericity correction. Other physiological data were compared using a similar two-way ANOVA without the region factor. Post hoc comparisons to localize the differences detected by a significant ANOVA were made using the Fisher Protected Least Significant Differences test. Data are reported as mean (SE).

RESULTS

The pH and $P_{a\text{CO}_2}$ values were appropriately different between ventilation groups, but similar for halothane- and isoflurane-anaesthetized animals (table I). Mean arterial pressure was 20% less for halothane-anaesthetized animals ($P < 0.001$) and the isoflurane-hypocapnia group had a greater mean arterial pressure than the normocapnic group, although all values were within the autoregulatory range [11]. Hypocapnia reduced area-weighted global CBF for both groups by 30% ($P < 0.001$), but there was no difference
Table 1. Physiological variables obtained at the time of determination of rCBF (mean (SE)). Significant effects: * anaesthetic; † hypocapnia; $ interaction. $\text{iso}^2\text{flurane}$ significantly greater than halothane during hypocapnia:

<table>
<thead>
<tr>
<th></th>
<th>Normocapnia</th>
<th>Hypocapnia</th>
<th>ANOVA</th>
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<tbody>
<tr>
<td></td>
<td>Halothane (n = 6)</td>
<td>Isoflurane (n = 7)</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.37 (0.05)</td>
<td>7.37 (0.02)</td>
<td></td>
</tr>
<tr>
<td>$P_{CO_2}$ (kPa)</td>
<td>5.6 (0.49)</td>
<td>5.4 (0.15)</td>
<td></td>
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<tr>
<td>$P_{O_2}$ (kPa)</td>
<td>21.1 (2.13)</td>
<td>14.9 (1.2)</td>
<td></td>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>72 (6)</td>
<td>80 (2)</td>
<td></td>
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<tr>
<td>Plasma glucose (mg dl$^{-1}$)</td>
<td>191 (14)</td>
<td>193 (14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Halothane (n = 6)</td>
<td>Isoflurane (n = 6)</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.53 (0.02)</td>
<td>7.55 (0.02)</td>
<td></td>
</tr>
<tr>
<td>$P_{CO_2}$ (kPa)</td>
<td>3.3 (0.12)</td>
<td>3.2 (0.12)</td>
<td></td>
</tr>
<tr>
<td>$P_{O_2}$ (kPa)</td>
<td>22.5 (1.87)</td>
<td>26.3 (1.73)</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>67 (4)</td>
<td>94 (4)</td>
<td></td>
</tr>
<tr>
<td>Plasma glucose (mg dl$^{-1}$)</td>
<td>185 (27)</td>
<td>160 (10)</td>
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Fig. 1. Comparison of area-weighted mean global CBF for halothane (■) and isoflurane ( □) groups during normo- and hypocapnia (mean, se). * Significantly different from normocapnia ($P < 0.05$).

This study has confirmed that halothane is a selective cortical vasodilator and demonstrates that this effect was present during both normo- and hypocapnia. Furthermore, the degree of hypocapnic reduction of CBF with both agents was similar in both cortical and subcortical structures.

There have been several reports on the effects of halothane and isoflurane on CBF in both animals [11–18] and humans [19–28]. There is debate on the relative effects of one agent compared with the other as far as relative vasodilating properties. This issue was reconciled partly by the report from Hansen and colleagues that, during normocapnia, halothane selectively dilated cortical but not subcortical structures relative to isoflurane. However, “whole-brain” CBF did not differ between the two agents [3]. They suggested that the CBF methodology chosen may determine whether or not one observes a difference between the two agents.
These authors also studied the flow–metabolism coupling during isoflurane or halothane anaesthesia and found that isoflurane selectively depressed cortical metabolism; they speculated that this was the cause of the relative vasodilatation by halothane in cortex [29]. Our results indirectly support their observations and assumptions. In our study there appeared to be no differential effect of one agent on carbon dioxide reactivity. As modest hypocapnia should not affect cerebral metabolic rate [30], if one assumes that the differing effects of halothane and isoflurane are...
caused by effects on local metabolic rates, one would postulate that manipulation of cerebrovascular resistance by hypocapnia would not alter flow distribution.

Compared with halothane, isoflurane appears to enhance cortical CBF reactivity to PaCO2 in the cat by intra-arterial xenon-133 washout [15] and in the rabbit by hydrogen clearance [17]. However, using the venous outflow technique, canine global CBF PaCO2 reactivity does not differ for the two agents [13]. There are a large number of studies in humans which have examined PaCO2 reactivity to either isoflurane or halothane [19–21, 24, 25, 27, 28] and one study comparing the agents during carotid endarterectomy [31]. All the human studies have reported quantitatively similar slopes of the carbon dioxide response line, using both cortical-weighted measures (xenon-133 washout) and whole-brain methods (Kety-Schmidt method). Our results suggest that cortical and subcortical carbon dioxide reactivity are similar in the carbon dioxide concentration range examined in this study. However, it should be noted that to compare most accurately quantitative differences in carbon dioxide reactivity for cortical and subcortical structures, one should use a repeated-measure CBF design for assessing individual subject reactivity, rather than looking at a slope of group means. Repeated measures of CBF is not possible at present with autoradiographic CBF determination. However, using data derived from the experimental design in our present study, it can be concluded that there is no effect of hypocapnia on the pattern of cortical vs subcortical flow distribution with the two agents.

Our reported values for global CBF should be interpreted cautiously, as the area-weighted method of estimating global CBF may bias the value towards the structures included in the sections used for the calculations. We adapted the method from that described by Hansen and colleagues [3] with the following modification: whereas they selected only forebrain structures that tended to be located centrally, we chose six sections placed approximately equidistant along the rostral–caudal axis of the brain. Despite the different method of choosing sections, our values for whole brain flow are similar. We observed a significant difference in the first (frontal cortex) section between halothane and isoflurane (although only at normocapnia), and attributed this to the preponderance of cortex in the sample. A surprising observation was that hindbrain values for CBF were greater with isoflurane than for halothane. The same was true for one of the more caudal local structures we examined, inferior colliculus. Hansen’s group did not examine hindbrain, but found no difference in inferior colliculus local CBF [3]. However, Maekawa and colleagues [16] described CBF distribution at different MAC multiples of isoflurane and, for 1 MAC isoflurane, reported CBF values for inferior colliculus and frontal cortex of 267 and 149 ml/100 g min−1, giving a ratio of 1.8, comparable to our ratio of 2.0 for the same structures. Mohamed and colleagues [32] used a rat preparation anaesthetized with 1.0% halothane to evaluate the effect of nimodipine on flow–metabolism coupling. In their vehicle-treated control group, they reported values for inferior colliculus and frontal cortex of 230 and 179 ml/100 g min−1, giving a ratio of 1.3, comparable to our ratio of 1.0. Although we know of no other published reports that compare directly the effects of halothane and isoflurane in caudal structures, there is some evidence that this differential effect between agents has been suggested previously. Although we have no good explanation for this selective effect of isoflurane, it is related presumably to a hindbrain metabolic effect.

Although, in animal studies of neurological outcome after incomplete regional [33] or focal [34] ischaemia, no difference exists between the influence of isoflurane and halothane, isoflurane has been associated with fewer ischaemic EEG changes during carotid endarterectomy than halothane [35, 36]. Therefore, the issue of whether or not isoflurane affords some degree of cerebral protection relative to halothane remains to be resolved. Regardless of the baseline differences in relative amounts of vasodilatation, differences in CBF reactivity to carbon dioxide could affect the clinical management of patients at risk for development of intraoperative cerebral ischaemia, such as during carotid endarterectomy. The use of induced hypocapnia may be beneficial when applied during the acute development of cerebral ischaemia during general anaesthesia [5]. We conclude that, in the rat, halothane is a selective cortical vasodilator and this effect is present at both normo- and hypocapnia. Furthermore, halothane and isoflurane have similar effects on cerebral carbon dioxide reactivity. The use of hypocapnia to promote "inverse steal" in the
presence of cerebral ischaemia should be effective with both agents.

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