CEREBRAL BLOOD FLOW AND METABOLISM DURING ISOFLURANE-INDUCED HYPOTENSION IN PATIENTS SUBJECTED TO SURGERY FOR CEREBRAL ANEURYSMS

J. B. MADSEN, G. E. COLD, E. S. HANSEN, B. BARDRUM AND C. KRUSE-LARSEN

Isoflurane decreases the cerebral metabolic rate for oxygen (CMRO₂) (Cucchiara, Theye and Michenfelder, 1974; Newberg, Milde and Michenfelder, 1983; Newman, Gelb and Lam, 1986); cerebral blood flow (CBF) is either unaltered (Todd and Drummond, 1984) or increased (Cucchiara, Theye and Michenfelder, 1974; Murphy et al., 1974; Eintrei, Leszniewski and Carlsson, 1985). Some controversy exists concerning the effects of isoflurane on intracranial pressure (ICP); in some studies little or no effect has been observed (Adams et al., 1981; Campkin, 1984); in a more recent study an increase in ICP was obtained (Grosslight et al., 1985). Comparative studies of the effects of halothane or isoflurane (Murphy et al., 1974; Todd and Drummond, 1984; Eintrei, Leszniewski and Carlsson, 1985) suggest that, although isoflurane has a less marked vasodilatory effect on cerebral blood vessels, it causes a more marked suppression of oxygen consumption (Todd and Drummond, 1984). During isoflurane-induced hypotension to a mean arterial pressure (MAP) of 40 mm Hg the concentrations, in cerebral tissue, of ATP, phosphocreatine, lactate and pyruvate did not change significantly, indicating the persistence of aerobic metabolism (Newberg, Milde and Michenfelder, 1984).

The aims of the present study were to determine the effects of isoflurane-induced hypotension — during craniotomy for cerebral aneurysm — on CBF and CMRO₂, during the pre-, per and post-hypotensive periods.

PATIENTS AND METHODS

Patients

CBF and CMRO₂ were measured in 10 patients subjected to surgery for the elective clipping of a cerebral aneurysm during isoflurane-induced hypotension. The craniotomy was performed 5–13 days after the subarachnoid haemorrhage.
mean age of the patients was 41 yr (range 30–62 yr) and the mean weight 67.5 kg (range 50–92 kg). All gave informed consent and the study was approved by the local scientific ethics committee. All the patients were awake and conscious without peripheral neurological deficits (Hunt and Hess grade I–II) (Hunt and Hess, 1968).

**Anaesthesia**

One hour before the induction of anaesthesia the patients were premedicated by mouth with diazepam 5 mg/25 kg body weight. Anaesthesia was induced with thiopentone 5–7 mg kg$^{-1}$ i.v. supplemented with fentanyl 0.2 mg i.v. Pancuronium 0.10–0.15 mg kg$^{-1}$ i.v. was administered. Isoflurane (inspired concentration 0.75%) was used to maintain anaesthesia, supplemented with 67 % nitrous oxide in oxygen. Fentanyl 0.1 mg was given before skin incision. In three patients additional doses (2 mg) of pancuronium were administered during the anaesthetic to maintain neuromuscular blockade. Ventilation was controlled throughout (Servo ventilator 900 B, Siemens Elema, Sweden) and end-expiratory carbon dioxide concentration monitored (Siemens Elema, Sweden). The vaporizer (Dräger Technic AG, Lübeck, West Germany) was calibrated before the study. Mean arterial pressure (MAP) was monitored and recorded (Servigor, BBC Goerz, Austria). Arterial blood-gas tensions were measured (ABL 1, Radiometer, Denmark), and $P_{aCO_2}$ was maintained greater than 100 mm Hg. Simultaneously with the opening of the dura, hypotension was induced by increasing the isoflurane concentration until MAP averaged 50–60 mm Hg. Shortly after clipping of the aneurysm, the isoflurane concentration was reduced to 0.75%.

**Measurements of cerebral blood flow**

In each patient three peroperative measurements of CBF were performed, before, during and after isoflurane-induced hypotension. Before surgery the internal jugular vein contralateral to the aneurysm was cannulated using the anterior approach, and a catheter was placed at the base of the skull (confirmed by x-ray). Simultaneously, a cannula was inserted to the dorsalis pedis or radial artery to permit direct pressure measuring and the aspiration of blood. Xenon-133, 3 mCi in saline was infused i.v. over a period of 20 min to obtain saturation of brain tissue.

Two-millilitre blood samples were drawn from the artery and the jugular vein at exact time intervals of 20 min during the saturation period and at 1, 2, 3, 4, 5, 7, 9, 11, 13, 15, 18, 20, 25 and 30 min during the desaturation period. The radioactivity in the samples was counted and the arterial and venous desaturation curves were drawn.

CBF was calculated using the height-over-area formula ($CBF_{30}$), and CMRO$_2$ from the product of CBF and the arterio-venous oxygen content difference ($CAO_2 - CVO_2$), which was measured in triplicate during each flow (OSM-2, Radiometer, Denmark). This i.v. modification of the classical Kety–Schmidt method (Kety and Schmidt, 1948) has recently been described in detail (Astrup et al., 1984; Bendtsen et al., 1985). The first CBF measurement was performed about 1 h after the induction of anaesthesia. A 20-min period of stable hypotension at a constant inspiratory isoflurane concentration was allowed before the flow measurement was repeated. The third determination of CBF was undertaken about 30 min after reducing the inspired isoflurane concentration to 0.75%. The data are presented in the text and table I as mean ± SEM, and a $P$ value < 0.05 was considered significant. The Wilcoxon test for paired data was used.

**RESULTS**

In all patients the operative conditions were excellent. There was no evidence of brain herniation; mannitol was not used. The patients recovered uneventfully and regained consciousness rapidly. One week and 1 month after the operation all the patients had recovered without neurological deficit. The desired level of hypotension was achieved 14 min (range 10–17 min) after the change in the isoflurane concentration. The level of hypotension was stable and only minor adjustments in isoflurane concentration were necessary. The average duration of hypotension was 62 min (range 36–117 min). During the posthypotensive period a stable MAP was achieved after 6.5 min (range 3–16 min).

During the prehypotensive period, CBF and CMRO$_2$ averaged 34.3 ± 2.1 ml/100 g min$^{-1}$ and 2.32 ± 0.16 ml/100 g min$^{-1}$ at MAP 74.5 ± 2.2 mm Hg and $P_{aCO_2}$ 4.1 ± 0.1 kPa. During the hypotensive period MAP averaged 54.6 ± 1.2 mm Hg and $P_{aCO_2}$ 3.97 ± 0.2 kPa. The isoflurane concentration was 2.2 ± 0.2 %. A significant decrease in CMRO$_2$ was noted ($P < 0.05$)
(table I), while a non-significant increase in CBF was observed. After the clipping of the aneurysm the isoflurane concentration was returned to 0.75 %. In comparison with the prehypotensive values, MAP and CMRO were unchanged, whereas CBF was significantly greater ($P < 0.05$) (table I).

**DISCUSSION**

In patients with subarachnoid haemorrhage who would be classified as grade I—II according to the criteria of Hunt and Hess (1968), CBF and CMRO were significantly decreased compared with values obtained in awake normal subjects (Voldby, Enevoldsen and Jensen, 1985a).

In a recent study of CBF and CMRO during surgery for cerebral aneurysm in patients subjected to 1 % isoflurane in an oxygen—air mixture, CBF and CMRO were 49.1 ml/100 g min$^{-1}$ and oxygen 2.0 ml/100 g min$^{-1}$, respectively, at MAP 78 mm Hg and $P_{CO_2}$ 4.4 kPa (Newman, Gelb and Lam, 1986). This difference in CBF compared with the present study might be caused by a difference in concentration in isoflurane (0.75 % v. 1.0 %); by the use of mannitol before induction in the cited study, since mannitol is known to increase CBF (Mendelow et al., 1985); because nitrous oxide was avoided; or because of a desaturation period of 15 min, compared with the 30 min used in the present study.

During the hypotensive period a significant decrease in CMRO from 2.32 to 1.73 ml/100 g min$^{-1}$ was observed, while CBF was unchanged. The change in CMRO represents a 48 % decrease compared with the awake state, and this finding accords with the decrease in CMRO observed during isoflurane-induced hypotension to MAP 51 mm Hg using 2.3 % isoflurane (Newman, Gelb and Lam, 1986). The decrease in CMRO in association with an unchanged CBF obtained during the hypotensive period also is in accordance with the findings of Newman, Gelb and Lam (1986). These findings are associated with a decrease in $(CaO_2 - CvO_2)$ and an increase in oxygen saturation of jugular venous blood, indirectly indicating an increase in oxygen tension of cerebral tissue. Animal studies on isoflurane-induced hypotension support these findings (Seyde and Longnecker, 1986).

Previous studies, and that presented here, suggest that isoflurane-induced hypotension induces a significant decrease in CMRO, while CBF is unaffected. Experimental studies suggest that the decrease in CMRO might protect the brain against ischaemia. These observations, together with studies of cerebral autoregulation showing partially intact autoregulation during isoflurane anaesthesia (Todd and Drummond, 1984), and studies in dogs (Artru, 1986) indicating partial preservation of carbon dioxide reactivity, suggest that isoflurane has a place during surgery for intracranial space-occupying lesions, and that isoflurane might be an alternative to sodium nitroprusside and other drugs during craniotomy for surgery on cerebral aneurysm. However, during the acute stage of subarachnoid haemorrhage, impairment of cerebral autoregulation has been found (Kamiya, Kuyama and Symon, 1983; Voldby, Enevoldsen and Jensen, 1985b). Therefore, induced hypotension at this time may be dangerous and effects different to those found in

<table>
<thead>
<tr>
<th>Cerebral haemodynamic values</th>
<th>Before hypotension</th>
<th>Hypotension</th>
<th>After hypotension</th>
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</thead>
<tbody>
<tr>
<td>Mean inspired isoflurane concentration (%)</td>
<td>0.75</td>
<td>2.2 ± 0.2*</td>
<td>0.75</td>
</tr>
<tr>
<td>Mean arterial pressure (MAP) (mm Hg)</td>
<td>74.5 ± 2.2</td>
<td>54.6 ± 1.2*</td>
<td>77.2 ± 3.5</td>
</tr>
<tr>
<td>$P_{CO_2}$ (kPa)</td>
<td>4.1 ± 0.1</td>
<td>4.0 ± 0.2</td>
<td>4.1 ± 0.2</td>
</tr>
<tr>
<td>Central temperature (°C)</td>
<td>36.5 ± 0.1</td>
<td>36.0 ± 0.3*</td>
<td>35.6 ± 0.3*</td>
</tr>
<tr>
<td>Cerebral blood flow (CBF) (ml/100 g min$^{-1}$)</td>
<td>34.3 ± 2.1</td>
<td>39.1 ± 5.0</td>
<td>40.7 ± 3.3*</td>
</tr>
<tr>
<td>Cerebral metabolic rate for oxygen (CMRO)</td>
<td>2.32 ± 0.16</td>
<td>1.73 ± 0.16*</td>
<td>2.14 ± 0.24</td>
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*P < 0.05 compared with the prehypotensive values (paired t test)
this study (carried out after the 5th day), could be anticipated.

In the posthypotensive period a significant increase in CBF — as compared with the prehypotensive period — was observed. This increase was not associated with changes in MAP or $P_{ac}CO_2$, suggesting that loss of autoregulation, or changes in cerebrovascular resistance, influenced these findings. This observation is in conflict with other studies in man in which posthypotensive hyperaemia was not observed (Newman, Gelb and Lam, 1986). However, studies in baboons suggest that a posthypotensive increase in CBF does occur (Van Aken et al., 1985), but the significance of this hyperaemia has not been studied. An explanation could be a direct effect of isoflurane, and that isoflurane was still present in the cerebral tissue at the time of the third CBF measurement. Studies in animals indicate that the desaturation of isoflurane in brain tissue is not completed for at least 20 min (Lam, Brown and Manninen, 1986).

The present study of isoflurane-induced hypotension supports a recent study of CBF and CMR$_O_2$, indicating that CMR$_O_2$, decreases and CBF is well maintained during the hypotensive period. These studies, together with animal studies, indicate that isoflurane may be preferred to halothane, nitroprusside and trimethapam. However, the evidence of moderate hyperaemia found in the postoperative period in the present study requires further evaluation.

REFERENCES


