

# The Effect of Isoflurane on Cerebral Blood Flow and Metabolism in Humans during Craniotomy for Small Supratentorial Cerebral Tumors

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Fourteen patients were studied during craniotomy for small supratentorial cerebral tumors. Cerebral blood flow (CBF) and cerebral metabolic rate of oxygen (CMRO<sub>2</sub>) were measured twice by a modification of the Kety-Schmidt technique using <sup>133</sup>Xe intravenously. Anesthesia was induced with thiopental 5-7 mg · kg<sup>-1</sup>, fentanyl 0.2 mg, and pancuronium, and maintained with 0.75% inspired isoflurane concentration in 67% nitrous oxide, and moderate hypocapnia. In one group of patients (n = 7), the inspired isoflurane concentration was maintained at 0.75% throughout anesthesia. One hour after induction of anesthesia, CBF and CMRO<sub>2</sub> averaged 31 ± 3 ml · 100 g<sup>-1</sup> · min<sup>-1</sup> and 2.1 ± 0.2 ml O<sub>2</sub> · 100 g<sup>-1</sup> · min<sup>-1</sup> (X ± SEM), respectively. During repeat studies 1 h later, CBF and CMRO<sub>2</sub> were unchanged. In a second group of patients (n = 7), an increase in the inspired isoflurane concentration from 0.75% to 1.5% was associated with a significant decrease in CMRO<sub>2</sub> from 2.4 ± 0.1 to 1.9 ± 0.1 ml O<sub>2</sub> · 100 g<sup>-1</sup> · min<sup>-1</sup>, and no change in CBF. It is concluded that this anesthetic regimen is safe to use in patients with small supratentorial tumors in whom only a small midline shift has occurred. (Key words: Anesthesia; neurosurgical. Anesthetics, volatile: isoflurane. Brain: blood flow; metabolism.)

THE EFFECT OF ISOFLURANE on cerebral hemodynamics and metabolism has been studied extensively in animals.<sup>1-4</sup> Isoflurane causes a dose-dependent increase in CBF due to cerebral vasodilation<sup>4,5</sup> and a decrease in CMRO<sub>2</sub>.<sup>1,4</sup> However, compared to halothane, isoflurane is less of a cerebral vasodilator,<sup>4</sup> and the decrease in CMRO<sub>2</sub> and the suppression of the cerebral electrical activity (EEG) are more pronounced.<sup>1,6</sup>

Only a few studies concerning the effect of isoflurane on CBF in patients undergoing craniotomy have been published. One study of the effects of halothane, enflurane, and isoflurane on regional CBF<sup>7</sup> confirmed the results of animal experiments, that the increase in CBF was less pronounced during isoflurane anesthesia.<sup>4</sup>

However, no studies concerning both global CBF and CMRO<sub>2</sub> measured during craniotomy have been published. For that reason, we found it of interest to measure CBF and metabolism during isoflurane anesthesia, sup-

plemented with 67% nitrous oxide in patients undergoing craniotomy for small supratentorial cerebral tumors.

## Materials and Methods

### PATIENTS

CBF and CMRO<sub>2</sub> were measured in 14 patients with supratentorial cerebral tumors. Mean age of the patients was 57 yr (range 22-75 yr) and mean weight 70.5 kg (range 50-94 kg). The patients gave informed consent, and the study was approved by the scientific committee of Copenhagen City, and was in accordance with the Helsinki II declaration. Preoperatively, all the patients were awake, and, during 3-7 days before surgery, methylprednisolone in a daily dose of 160 mg was given orally. Patients with a shift of midline structure > 15 mm estimated by CT scanning, and those being treated for heart disease, hypertension or chronic pulmonary diseases, were excluded from the study. The age of the patients and the localization, size, and histological diagnosis of the tumors, together with the midline shift, are shown in table 1.

### ANESTHESIA

One hour before induction of anesthesia, the patients were premedicated with pentobarbital 100-150 mg i.m. After preoxygenation, anesthesia was induced with thiopental 5-7 mg · kg<sup>-1</sup>, fentanyl 0.1 mg, and pancuronium 0.15 mg · kg<sup>-1</sup>. The patients were manually hyperventilated until total paralysis. Approximately 1 min before tracheal intubation, lidocaine 1.5 mg · kg<sup>-1</sup> iv was given. Following tracheal intubation, anesthesia was maintained with isoflurane 0.75% and nitrous oxide 67% in oxygen supplemented with fentanyl 0.1-0.2 mg and pancuronium sufficient to provide total paralysis estimated by train-of-four stimulation.

Throughout anesthesia, the patients were ventilated by a Servo<sup>®</sup> 900 B ventilator (Siemens-Elma, Sweden), and moderate hypocarbia of approximately 30 mm Hg was achieved and monitored with arterial gas analyses (ABL-1<sup>®</sup>, Radiometer, Denmark). The PaO<sub>2</sub> was maintained >100 mm Hg. Mean arterial blood pressure (MABP) was recorded with the transducer technique (Servogor 330<sup>®</sup>, BBC Goerz, Austria). Rectal temperature

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TABLE 1. Patient Profile.

Patient No.	Age (yr)	Location of the Tumor	Histological Diagnosis	Midline Shift (mm)	Maximum Area of the Tumor (cm <sup>2</sup> )
<b>Group 1</b>					
1	35	Frontal lobe	Oligodendroglioma	0	6
2	66	Parietal lobe	Metastasis	11	11
3	71	Frontal lobe	Meningeoma	0	8
4	33	Frontal lobe	Oligodendroglioma	4	3
5	50	Frontal lobe	Astrocytoma	0	2
6	58	Parietal lobe	Oligodendroglioma	0	1
7	67	Frontal lobe	Oligodendroglioma	5	7
	54 ± 6			3 ± 2	5 ± 2
<b>Group 2</b>					
1	39	Frontal lobe	Oligodendroglioma	4	17
2	66	Frontal lobe	Meningeoma	0	13
3	21	Parietal lobe	Meningeoma	6	15
4	56	Frontal lobe	Adenoma	0	6
5	47	Frontal lobe	Oligodendroglioma	3	8
6	75	Parietal lobe	Metastasis	14	13
7	62	Frontal lobe	Lymphoma	8	20
	52 ± 8			5 ± 2	13 ± 2*

Age, location, histological diagnosis of the tumor, and midline shift evaluated by CT-scanning. Mean ± SEM are indicated.

\* Significant difference between the groups.

was measured continuously. The patients were divided into two groups. In group 1 (n = 7), the inspiratory isoflurane concentration remained at 0.75% throughout the anesthesia, and two CBF measurements were performed. In group 2 (n = 7), the isoflurane concentration was increased from 0.75% to 1.5% immediately after the first CBF measurement and the flow measurement was repeated.

#### MEASUREMENT OF CBF AND CMRO<sub>2</sub>

After induction of anesthesia, the internal jugular vein contralateral to the side of the tumor was punctured, and a catheter advanced until its tip, confirmed by x-ray, was placed at the base of the skull. CBF was measured using <sup>133</sup>Xenon. The brain was saturated during a 20-min period with <sup>133</sup>Xenon using a continuous intravenous infusion at a constant rate. Three mCi dissolved in 25 ml of saline were used. Blood samples of 2 ml were withdrawn from the arterial and the jugular venous catheter at 16, 18, and 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 radioactive xenon was vented through the central suction. The sample radioactivity was counted in a well counter (Palle Medicotechnic, Denmark). Average blood flow through the brain during the desaturation period, CBF<sub>30</sub>, was calculated by the height-over-area formula of Kety-Schmidt,<sup>8</sup> using a xenon blood-brain partition coefficient of 1.1. This method has previously been reported.<sup>9,10</sup>

CMRO<sub>2</sub> was calculated from the product of CBF and the arteriovenous oxygen difference (AVDO<sub>2</sub>).

The oxygen content in arterial and jugular venous blood was calculated from the formula: oxygen content = 1.39 · hemoglobin (g · 100 g<sup>-1</sup>) · % saturation (a-v) O<sub>2</sub> + 0.03 · PaO<sub>2</sub> (mmHg). Oxygen saturation was determined photometrically (Hemoximeter B<sup>®</sup>, OSM-2, Radiometer, Denmark), PaO<sub>2</sub> (ABL-1<sup>®</sup>, Radiometer, Denmark) and hemoglobin concentration was measured directly (Hemalog 8<sup>®</sup>, Technicon Autoanalyser). The first CBF measurement in group 1 and 2 was performed 67 ± 8 min and 73 ± 6 min, respectively, after induction of anesthesia, and about 15 min before surgery was started. The second flow measurement in the two groups was performed 60 min later. Before the second flow measurement in group 2, the inspired isoflurane concentration was kept constant at 1.5% for 30 min.

The cerebrovascular reactivity to changes in PaCO<sub>2</sub> was tested by further hyperventilation following the second flow measurement. The change in CBF was measured indirectly. Assuming that CMRO<sub>2</sub> is constant during the hyperventilation period, CBF is inversely proportional to AVDO<sub>2</sub>.<sup>11,12</sup> PaCO<sub>2</sub> and AVDO<sub>2</sub> were measured before and 5 min after hyperventilation, and the percentage change in AVDO<sub>2</sub> was calculated and expressed as percentage change in CBF. The relative CBF response to hyperventilation was defined as percent CBF change per mmHg of Δ PaCO<sub>2</sub>.<sup>13,14</sup>

The results in text and tables are expressed as mean ± standard error of mean (SEM). Comparisons between the values were performed using Student's *t* test for paired and unpaired data when appropriate. Initial CBF and CMRO<sub>2</sub> values were compared with the degree of midline shift of the tumor and the size of the tumor, respectively,

TABLE 2. Effect of Isoflurane on Blood Pressure, CBF, and CMRO<sub>2</sub>

	Inspired Isoflurane Conc. %	Body Temp. (°C)	PaCO <sub>2</sub> (mmHg)	Mean Arterial Blood Pressure (mmHg)	CBF (ml · 100 g <sup>-1</sup> · min <sup>-1</sup> )	CMRO <sub>2</sub> (ml O <sub>2</sub> · 100 g <sup>-1</sup> · min <sup>-1</sup> )
Group 1 (n = 7)						
Flow 1	0.75	35.7 ± 0.2	31 ± 2	73 ± 5	31 ± 3	2.1 ± 0.2
Flow 2	0.75	35.1 ± 0.2*	29 ± 1	66 ± 5	29 ± 3	2.0 ± 0.2
Group 2 (n = 7)						
Flow 1	0.75	35.7 ± 0.2	31 ± 2	82 ± 4	35 ± 2	2.4 ± 0.1
Flow 2	1.5	35.4 ± 0.2*	30 ± 2	67 ± 6*	33 ± 4	1.9 ± 0.1*

\* Statistical difference within the groups ( $P < 0.05$ ). No statistical differences were found between the groups.

using linear correlation analysis. A  $P$  value less than 0.05 was considered significant.

### Results

#### CBF, CMRO<sub>2</sub>, AND MABP

No statistically significant differences with respect to age, weight, and degree of midline shift of the tumors were found. The area of the tumors was significantly larger in group 2 patients (table 1).

During the first CBF measurement in group 1 and 2, where anesthesia was maintained with 0.75% isoflurane, CBF averaged  $31 \pm 3$  and  $35 \pm 2$  ml · 100 g<sup>-1</sup> · min<sup>-1</sup>, respectively (n.s.) During repeat studies 1 h later, CBF did not change significantly from these values (table 2). During the first flow measurement in the two groups, CMRO<sub>2</sub> averaged  $2.1 \pm 0.2$  and  $2.4 \pm 0.1$  ml O<sub>2</sub> · 100 g<sup>-1</sup> · min<sup>-1</sup>, respectively (n.s.). In group 1, CMRO<sub>2</sub> was unchanged by repeat studies 1 h later (n.s.). In group 2, increasing isoflurane inspired concentration was associated with a significant decrease in CMRO<sub>2</sub> to  $1.9 \pm 0.1$  ml O<sub>2</sub> · 100 g<sup>-1</sup> · min<sup>-1</sup> ( $P < 0.05$ ) (table 2).

The change in isoflurane concentration from 0.75% to 1.5% was associated with a significant decrease in MABP from  $84 \pm 4$  to  $67 \pm 6$  mmHg ( $P < 0.05$ ). Furthermore, in both groups, a significant decrease in body temperature was observed ( $P < 0.05$ ).

Initial CBF and CMRO<sub>2</sub> values were correlated to the degree of midline shift and to the size of the tumor; no statistically significant correlation was found.

TABLE 3. Relative CBF Response to Hyperventilation Defined as Percent CBF Change per mmHg of  $\Delta$ PaCO<sub>2</sub> in the Two Groups

	$\Delta$ PaCO <sub>2</sub> (mmHg)	Relative Reactivity (% $\Delta$ CBF/ $\Delta$ PaCO <sub>2</sub> ) (% · mmHg <sup>-1</sup> )
Group 1	6 ± 1	4.4 ± 1.0
Group 2	4 ± 1	5.1 ± 0.9

Mean ± SEM. No statistical difference was found between the values in the two groups.

The relative CBF response to hyperventilation averaged  $4.4 \pm 1.0\%$  · mmHg<sup>-1</sup> in group 1 patients, compared with  $5.1 \pm 0.9\%$  · mmHg<sup>-1</sup> in group 2 (n.s.) (table 3).

### Discussion

Cerebral blood flow was measured using an intravenous modification of the classical inhalation method described by Kety and Schmidt.<sup>8</sup> The validity of this technique for CBF measurement has recently been tested in awake patients with supratentorial cerebral tumors; CBF and CMRO<sub>2</sub> averaged  $47$  ml · 100 g<sup>-1</sup> · min<sup>-1</sup> and  $3.3$  ml O<sub>2</sub> · 100 g<sup>-1</sup> · min<sup>-1</sup>, respectively.<sup>9</sup> These values correspond to values found in normal man,<sup>8</sup> and argue against a major influence of the tumor on CBF. Furthermore, this technique has produced reliable results in repeated CBF studies with althesin<sup>10</sup> or etomidate.<sup>15</sup> CBF measured with this method represents global flow, because venous blood flow from each hemisphere is mixed in the confluence of the venous sinuses. Some methodological errors might occur from contamination by external jugular venous blood<sup>16</sup> and by central venous blood.<sup>17</sup> Regional flow differences have been observed in patients with cerebral tumors,<sup>18</sup> but the effect of the tumor on global flow is still not evident. In addition, in this study, flow measurements were performed in patients with small supratentorial cerebral tumors without a large midline shift. Furthermore, all the patients were alert preoperatively, and in good physical state.

In the present study, it is presumed that steady-state conditions were obtained during the 30-min desaturation period. This assumption was fulfilled as far as PaCO<sub>2</sub> is concerned; however, arterial pressure did increase in relation to the operative procedure, especially at the time of incision of the skin. In order to avoid this influence, surgical stimulation during the first 15 min of the desaturation period was avoided. This precaution would also prevent augmentation of CMRO<sub>2</sub>, which, according to Kuramoto *et al.*,<sup>19</sup> occurs during nociceptive stimulation in dogs. The second CBF measurement was performed during the evacuation of the tumor. At this time, noci-

ceptive stimulation induced by the surgery is of minor importance.

A dose-dependent decrease in MABP was observed in the present study. This observation was in accordance with others.<sup>20,21</sup> Hypotensive episodes were observed, especially during the period just before the start of the operative procedure. Infusions of lactated Ringer solution 1.5–2.0 l over a 20-min period before surgical stimulation was necessary to prevent severe hypotension. In one patient, MABP failed to increase after skin incision, and phenylephrine 7.5 mg iv was administered because of decrease in MABP below 55 mmHg.

Halothane dilates cerebral vessels and increases CBF and intracranial pressure. Thus, a dangerous decrease in cerebral perfusion pressure may occur.<sup>22</sup> In contrast, the effect of isoflurane on CBF is less pronounced, as shown in animal experiments<sup>4</sup> as well as in human studies.<sup>§</sup> These observations were confirmed in a recent human study of perioperative rCBF during craniotomy for cerebral tumors.<sup>7</sup> In this study, CBF did not increase after increasing isoflurane concentration. This is in contrast to other studies in animals<sup>5</sup> and humans,<sup>§</sup> where isoflurane induced a dose-dependent decrease in cerebral resistance associated with an increase in CBF. The difference might be explained by the fact that the cerebral vasodilatation is counteracted by the decrease in MABP; however, this assumption indicates that autoregulation was lost during the second flow measurement using 1.5% isoflurane. This mechanism, although not proven because cerebrovascular resistance or autoregulation was not tested, may be a reasonable explanation because the level of MABP was close to the lower level of autoregulation. Furthermore, it has been shown in animal experiments that cerebral autoregulation was impaired during higher concentrations of isoflurane.<sup>23</sup>

In a study similar to this, anesthesia was maintained with 1% isoflurane in oxygen-air mixture in patients subjected to surgery for cerebral aneurysms during isoflurane-induced hypotension;<sup>24</sup> global CBF and CMRO<sub>2</sub> averaged 49 ml·100 g<sup>-1</sup>·min<sup>-1</sup> and 2.0 ml O<sub>2</sub>·100 g<sup>-1</sup>·min<sup>-1</sup>, respectively. Compared with the present study, CBF was higher, while identical values of CMRO<sub>2</sub> were found. The higher CBF values might have been caused by the higher isoflurane concentration and by the use of mannitol before induction of anesthesia.<sup>24</sup> The low normal values of CBF observed in this study may be due to the hyperventilation. Furthermore, the lowered body temperature may also decrease metabolism, resulting in

a further decrease in the CBF values. The significant decrease in CMRO<sub>2</sub> observed in group 2 patients in this study is not assumed to be secondary by the decrease in temperature alone, as the fall in temperature is larger in group 1 patients.

During the flow measurements, a rather high concentration of nitrous oxide was used, which might influence CBF and metabolism. Although 70% nitrous oxide has a modest action on CBF and CMRO<sub>2</sub>,<sup>25</sup> it seems that there is a synergistic effect when nitrous oxide is used with halothane<sup>26</sup> or with isoflurane,<sup>27</sup> but a decrease of CBF when nitrous oxide is administered in association with an intravenous agent as diazepam.<sup>28</sup> In this study, intravenous agents as fentanyl and barbiturate were used together with isoflurane; therefore, it is difficult to define exactly to which extent nitrous oxide influenced CBF and metabolism.

In the present study, a dose-related decrease in CMRO<sub>2</sub> was observed, which is in agreement with animal and human studies.<sup>1,4,29</sup> The level of CMRO<sub>2</sub> in this study was comparable to results obtained in a recent study of continuous infusion of etomidate 60 µg·kg<sup>-1</sup>·min<sup>-1</sup> (1.8 ± 0.2 ml O<sub>2</sub>·100 g<sup>-1</sup>·min<sup>-1</sup>),<sup>15</sup> but higher than the values obtained during continuous infusion of althesin 0.5 ml·kg<sup>-1</sup>·h<sup>-1</sup> (1.5 ± 0.1 ml O<sub>2</sub>·100 g<sup>-1</sup>·min<sup>-1</sup>)<sup>10</sup> and during 0.5% halothane supplemented with thiopental 8 mg·kg<sup>-1</sup> (1.6 ± 0.2 ml O<sub>2</sub>·100 g<sup>-1</sup>·min<sup>-1</sup>).<sup>9</sup>

It is concluded that isoflurane supplemented with N<sub>2</sub>O during moderate hypocapnia is a reasonable choice in patients subjected to craniotomy for chronic small space-occupying lesions. During this combined anesthesia, an associated decrease in CBF and CMRO<sub>2</sub> has been found. CBF is maintained in spite of a dose-related decrease in MABP. Whether this is due to an intact autoregulation without a cerebral vasodilatation induced by isoflurane, or as a result of an impaired autoregulation where the decrease in MABP is counteracted by an isoflurane-induced cerebral vasodilatation, cannot be answered in this study, because cerebrovascular resistance and autoregulation were not tested.

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