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Cerebral Circulation and Metabolism during Enflurane Anesthesia in Humans

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The effects of enflurane anesthesia on cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMR_{O_2}) were studied in 17 patients. The patients were divided into two groups according to the depth of anesthesia. Cerebral perfusion pressure was maintained above 60 mmHg with phenylephrine. In Group 1 (arterial enflurane concentration, 15 mg/dl), patients were studied before surgery, while in group 2 (enflurane concentration, 27 mg/dl), the measurements were performed before and during surgery. In Group 1, mean CBF and CMR_{O_2} were 53 and 2.8 ml·100 g^{-1}·min^{-1}, respectively. These values were not significantly different from CBF (46 ml·100 g^{-1}·min^{-1}) and CMR_{O_2} (3.1 ml·100 g^{-1}·min^{-1}) values previously obtained in awake patients. In Group 2 before surgery, mean CBF and CMR_{O_2} were 61 and 2.6 ml·100 g^{-1}·min^{-1}, respectively, and were significantly different from the awake values, while the EEG showed frequent spikes and suppression. In Group 2 during surgery, mean CBF and CMR_{O_2} did not differ from the values obtained before surgery, despite significant EEG changes. The results indicate that enflurane is a cerebral vasodilator and causes an increase in CBF and a decrease in CMR_{O_2} in humans at an anesthetic level characterized by frequent spikes and suppression on the EEG. (Key words: Anesthetics, volatile: enflurane. Brain: blood flow, oxygen consumption.)

THE CEREBRAL EFFECTS of enflurane have been well documented in both electrophysiological and behavioral studies.[1–3] However, the effects of enflurane on cerebral blood flow (CBF) and oxygen consumption (CMR_{O_2}) have not been investigated thoroughly in humans. Wollman *et al.*[4] reported that CBF remained unchanged, while CMR_{O_2} decreased by 50% at a level of anesthesia characterized by frequent EEG spike activity separated by periods of electrical silence. However, subsequent study from the same laboratory, though published in abstract form only, revealed that enflurane, 1.1 MAC and 1.6 MAC, increased CBF by 37% and 80% from the awake values if blood pressure was supported.†† Rolly and Van Aken[5] recently reported significant decreases in regional CBF in frontal and occipital regions at 2% inspired enflurane anesthesia. However, in their study, patients were premedicated with meperidine and anesthesia was maintained in combination with 67% nitrous oxide. Hence, there may be drug interaction effects, which makes it difficult to evaluate the sole effect of enflurane on CBF. These discrepancies prompted us to examine the effect of enflurane at two different levels of anesthesia on CBF and CMR_{O_2} in humans and in addition to evaluate the CBF and CMR_{O_2} responses to surgical stimulation.

Methods

Seventeen ASA I or II patients (male, four; female, 13) who were undergoing elective surgery were studied. Age of patients ranged from 25 to 58 yr. The study was approved by the Hospital Committee on Human Study. Preoperative examination revealed no cardiopulmonary or neurologic disorders in all patients. Atropine sulfate, 0.5 mg, was given intramuscularly 30 min before induction. Anesthesia was induced with enflurane in oxygen, and the inspired concentration of enflurane was increased to 4% over 3–4 min. Endotracheal intubation was facilitated with intravenous administration of pancuronium bromide, 6–8 mg. After intubation, enflurane concentration was changed to either 2% in group 1 (seven patients) or 3.5% in group 2 (10 patients). In all patients ventilation was controlled mechanically to maintain normocapnia, and nitrogen was added to adjust the FI_{O_2} to 0.33. A 21-gauge teflon indwelling catheter was placed in the radial artery and an 18-gauge Medicut® catheter was placed in the jugular bulb for blood sampling and pressure measurement. The position of the jugular bulb catheter tip was confirmed by x-ray. In Group 1, measurements were made 30 min after starting enflurane inhalation, 2%. In Group 2, measurements were made 30 min after enflurane inhalation, 3.5%, (before surgery) and then 15–30 min after the start of abdominal surgery (during surgery). The rectal temperature was monitored by a calibrated thermistor probe and was kept at 36.8 ± 0.2° C using a cooling–warming water mattress. The end-expired carbon dioxide concentration was monitored continuously with an infra-red gas analyzer (Datex, Normocap, Denmark). Bilateral unipolar, frontal, and occipitotemporal electroencephalograms (EEG) were monitored and recorded continuously (Nihon Koden, MAF5,

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TABLE 1. Physiologic Variables and Anesthetic Concentration during Enflurane Anesthesia

	n	Enflurane concentration mg/dl	MAP mmHg	Pa_{O_2} mmHg	Pa_{CO_2} mmHg	pH
Group 1	7	A 14.5 ± 0.8 V 14.5 ± 0.7	81 ± 2*	135 ± 7*	38 ± 1	7.37 ± 0.02*
Group 2 (before surgery)	10	A 27.3 ± 1.0 V 27.0 ± 0.8	76 ± 3*	191 ± 32*	35 ± 1	7.41 ± 0.01*
Group 2 (during surgery)	10	A 27.3 ± 0.9 V 27.3 ± 0.8	80 ± 3*	177 ± 31*	37 ± 1	7.40 ± 0.01*
Awake†	13	A — — V — —	95 ± 4	473 ± 12	35 ± 1	7.45 ± 0.01

The values are mean ± SE.
A = Arterial blood; V = Jugular bulb blood.
* Significantly different from awake value ($P < 0.05$).
† Data from our laboratory (Br J Anaesth 48:545–550, 1976), FI_{O_2} during measurement = 0.85.

Japan). CBF was measured by the Kety-Schmidt technique using 15% nitrous oxide as previously reported.[6] After taking arterial and jugular bulb venous blood samples, nitrous oxide 15% was added to the gas mixture and the nitrogen concentration was adjusted to maintain a constant FI_{O_2} at 0.33. Simultaneous arterial and jugular bulb venous blood samples then were obtained at 1, 2, 3, 4, 5, 7, 9, 12, and 15 min after the initiation of nitrous oxide. The concentration of nitrous oxide in the blood was measured by gas chromatography (Shimazu, GC-4APTF, Japan). The CBF was calculated by a modification of the Kety-Schmidt method, which includes prolongation of the nitrous oxide saturation phase and extrapolation of the arterio-venous difference of nitrous oxide concentration to infinity. The arterial and internal jugular venous pressures were measured by strain gauge transducers with the zero point at the mastoid process and were recorded on a polygraph (Nihon Koden, MAF5, Japan). The electrocardiogram (lead II) also was monitored. The difference between mean arterial pressure (MAP) and mean jugular venous pressure was defined as cerebral perfusion pressure (CPP). Cerebral vascular resistance (CVR) was calculated as the ratio of CPP to CBF. P_{O_2}, P_{CO_2}, and *p*H were measured with a blood gas analyzer (ABL2, Radiometer, Denmark). Oxygen saturation and hemoglobin concentration were measured with an IL CO-oximeter (Model 282, Instrumentation Laboratory, Lexington, MA). Blood glucose concentration was measured by an enzymatic method. These values were measured before and at 5, 10, and 15 min after the start of nitrous oxide inhalation; the mean values of the four samples are reported. Arterial and jugular bulb venous blood concentrations of enflurane were measured with a gas chromatograph (Shimazu, GC-4APTF, Japan) equipped with a flame ionization detector. Enflurane in the blood was extracted into carbon tetrachloride, and the recovery rate of enflurane was 98 ± 1 per cent. The values reported are the mean of three samples taken before and 5 and 15 min after initiating the inhalation of nitrous oxide. Oxygen content was calculated from the hemoglobin oxygen-carrying capacity and the amount of dissolved oxygen, as estimated from P_{O_2} and oxygen solubility. CMR_{O_2} and GMRglucose were calculated as the product of CBF and the oxygen or glucose content differences, respectively, between the arterial and the jugular bulb blood. Oxygen–glucose index was calculated as suggested by Cohen *et al.*[7] CPP was maintained above 60 mmHg with an infusion of phenylephrine (0.005% solution); 0.4 ± 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in Group 1 and 1.3 ± 0.3 and 0.9 ± 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in Group 2 before and during surgery, respectively. Phenylephrine was chosen because it has been shown to have no effect on CBF or CMR_{O_2}.[8] If CPP fell below 60 mmHg despite phenylephrine infusion or if CPP fluctuated more than 10% from the mean value obtained during inhalation of nitrous oxide, the data were discarded. In Group 2, in order to quantify the EEG change, the frequency of spikes (greater than 100 μV, less than 0.08 s duration), sharp waves (greater than 100 μV, 0.08– 0.2 s duration), spike-and-wave complex, and the percentage of time occupied by the periods of suppression (electrical silence 1 s in duration or longer) were determined during the 15-min period of CBF measurement. The analysis was done visually without knowledge of surgical stimulation.

Statistical differences were tested by one-way analysis of variance with critical-difference testing, except the EEG analysis, which was tested by Wilcoxon's rank sum test. $P < 0.05$ was considered significant.

Results

Physiologic variables in each group are summarized in table 1 and compared with awake values previously obtained in our laboratory.[6] The variations in the blood concentrations of enflurane from the tabulated mean values (table 1) during measurements were 0.9 ± 0.1 mg/dl (group 1), 0.9 ± 0.1 mg/dl (Group 2, before surgery) and 1.0 ± 0.1 mg/dl (Group 2, during surgery), respec-

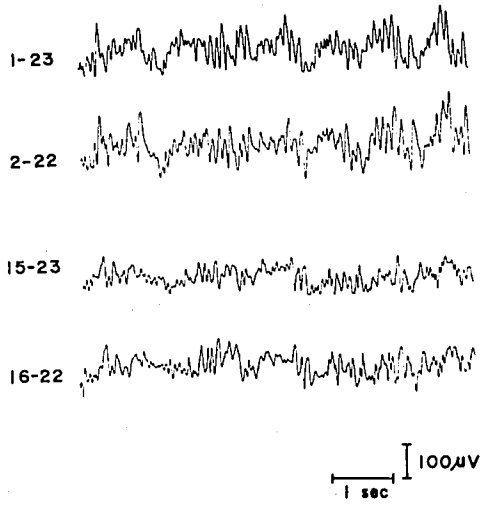

FIG. 1. Representative electroencephalogram during enflurane anesthesia (Group 1). Predominant 12–15 Hz of 50–100 μV waves were observed with higher amplitude in frontal leads than in occipitotemporal leads (anterior dominance). CBF and CMR_{O_2} were 56.7 ml·100 g^{-1}·min^{-1} and 3.0 ml·100 g^{-1}·min^{-1}, respectively. Enflurane concentration in the arterial blood was 16.8 mg/dl and Pa_{CO_2} was 39 mmHg.

tively. Preanesthetic MAP and heart rate were 91 ± 6 mmHg and 63 ± 2/min in Group 1 and 90 ± 4 mmHg and 73 ± 3/min in Group 2. Pa_{O_2} was maintained above 100 mmHg, and Pa_{CO_2} and *p*H were within the normal range. The mean rectal temperature in the present study (36.8° C) was 0.6° C higher than the awake group (36.2° C) in which nasopharyngeal temperature was measured. There was no significant difference in age between the groups.

EEG recordings in Group 1 showed predominant 12–15 Hz activities with amplitude of 50–100 μV in 5 of 7 patients, while in the remaining two, 8–10 Hz activities with amplitude of 25 to 50 μV were predominant. In all patients anterior dominance[9] was observed. A representative EEG from Group 1 is shown in figure 1. Before surgery in Group 2, the EEG showed frequent spikes and suppression. With surgical stimulation, frequencies of spike and spike-and-wave complex were decreased, and suppression disappeared in most cases. A representative EEG from Group 2 is shown in figure 2. Table 2 shows the results of EEG analysis in Group 2.

Cerebral circulatory and metabolic variables are summarized in table 3. CPP was slightly lower in Groups 1 and 2 as compared with the awake values. There was no significant difference in CBF between Group 1 and the awake group. However the mean CBF in Group 2 before and during surgery was 33 and 46% greater, respectively, than that of the awake group. The mean CVR decreased significantly in Groups 1 and 2 as compared with the awake values.

There was no significant difference in CMR_{O_2} between Group 1 and the awake group. However, the mean CMR_{O_2} in Group 2 before surgery was 17% less than that of the awake group and remained unchanged with surgical stimulation.

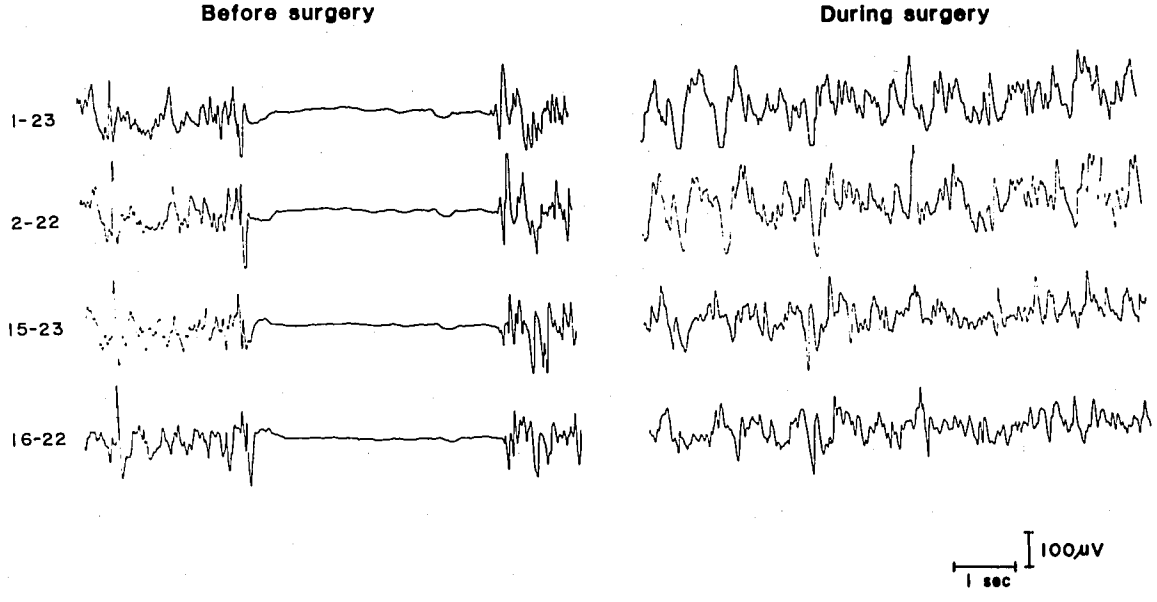

FIG. 2. Representative electroencephalogram during enflurane anesthesia (Group 2). Frequent spikes and suppression observed before surgery (*left*) disappeared during surgery (*right*). CBF and CMR_{O_2} before and during surgery were 60 ml·100 g^{-1}·min^{-1} *vs.* 72 ml·100 g^{-1}·min^{-1} and 2.6 ml·100 g^{-1}·min^{-1} *vs.* 2.4 ml·100 g^{-1}·min^{-1}, respectively. Enflurane concentration and Pa_{CO_2} before and during surgery were 26.5 mg/dl *vs.* 25.8 mg/dl and 34 mmHg *vs.* 36 mmHg, respectively.

TABLE 2. Electroencephalographic Changes with Surgical Stimulation during Enflurane Anesthesia (Group 2)

	Before Surgery	During Surgery
Spike frequencies/min	17 ± 2	9 ± 2*
Spike and wave frequencies/min	4 ± 1	1 ± 1*
Sharp wave frequencies/min	11 ± 2	13 ± 2
Suppression (%)	10 ± 2	1 ± 1*

The values are mean ± SE.
* Significantly different from the value before surgery ($P < 0.05$).

The mean CMR glucose tended to decrease in both Groups 1 and 2 as compared with the awake values. There was no significant change in oxygen–glucose index in any group. Jugular venous P_{O_2} was significantly higher in Group 2 than in the awake group.

Discussion

The Kety–Schmidt method for measuring CBF and CMR_{O_2} in awake humans has been used for several decades and values have been reported from numerous laboratories. The range of normal values for CBF and CMR_{O_2} are from 43 to 54 ml · 100 g^{-1} · min^{-1} and from 3.0 to 3.3 ml · 100 g^{-1} · min^{-1}, respectively.[8,10,11] Since our previously reported values are within this reported range and our methodology has not changed, we could not justify the risk and expense of repeating control measurements in awake patients at this time. Accordingly, we used our awake values obtained previously for comparison.

The present study demonstrated that in humans enflurane causes an increase in CBF (when CPP is maintained above 60 mmHg) at a level of anesthesia characterized by frequent spikes and suppression on the EEG. The increase in CBF was accompanied by a reduction in CVR, indicating that enflurane is a cerebral vasodilator. In Group 1, the significant reduction in calculated CVR was largely due to a decrease in CPP rather than any significant change in CBF. Wollman *et al.*[4] reported no significant change in CBF in volunteers during enflurane anesthesia when the EEG showed frequent spikes separated by periods of electrical silence. A subsequent study from the same laboratory by Murphy *et al.* demonstrated that CBF did not change significantly at 0.6 MAC enflurane but with arterial blood pressure support increased by 37 and 80% at 1.1 and 1.6 MAC, respectively, as compared with the awake values. For comparison, MACs in Groups 1 and 2 in the present study calculated from the arterial blood concentrations of enflurane (assuming a blood gas partition coefficient of 1.91 and a MAC for enflurane of 1.68%[12,13]) were 0.6 and 1.2 MAC, respectively. However, actual MAC values must have been slightly higher because of additional factors, which contribute to the difference in the estimation of arterial and end-tidal anesthetic concentration.[14] Thus, the anesthetic levels in our patients may have been comparable with those in the study by Murphy *et al.* and, therefore, the increase in CBF with arterial blood pressure support observed in the present study is in agreement with their results. The decrease in regional CBF reported by Rolly and Van Aken[5] could be the result of the combined effects of enflurane, nitrous oxide and meperidine, and/or a decrease in MAP to approximately 60 mmHg.

Studies in the dog indicated that hemispheric CBF was either increased or unchanged with enflurane.[15,16] This difference also could be explained by the fact that the reduction in CPP was greater in the report where CBF did not increase.[16] From these considerations, we believe that the effect of anesthetics on CBF must be evaluated when CPP is maintained.

Wollman *et al.*[4] found a 50% reduction in CMR_{O_2} with enflurane anesthesia, while the EEG showed frequent spikes and suppression. This is the largest decrease ever reported in humans for a volatile anesthetic. However, Murphy *et al.*, from the same laboratory subsequently reported that CMR_{O_2} was unchanged or slightly decreased during enflurane anesthesia (0.6, 1.1, 1.6 MAC), though they did not present the actual values. Therefore, one can not draw any definite conclusions from their studies regarding the cerebral metabolic effects of enflurane in

TABLE 3. Cerebral Circulation and Metabolism during Enflurane Anesthesia

	n	CPP mmHg	CBF ml · 100 g^{-1} · min^{-1}	CMR_{O_2} ml · 100 g^{-1} · min^{-1}	CVR mmHg · ml^{-1} · 100 g · min	CMR glucose mg · 100 g^{-1} · min^{-1}	Oxygen–Glucose Index (%)	Jugular Venous P_{O_2} mmHg
Group 1	7	73 ± 2*	53 ± 3	2.8 ± 0.1	1.4 ± 0.1*	4.2 ± 0.6	100 ± 13	42 ± 1
Group 2 (before surgery)	10	66 ± 3*	61 ± 4*	2.6 ± 0.1*	1.1 ± 0.1*	3.9 ± 0.4	96 ± 9	48 ± 2*
Group 2 (during surgery)	10	71 ± 3*	67 ± 4*†	2.6 ± 0.1*	1.1 ± 0.1*†	3.9 ± 0.4	97 ± 7	51 ± 2*†
Awake‡	13	90 ± 3	46 ± 2	3.1 ± 0.2	2.0 ± 0.1	5.0 ± 0.5	88 ± 10	41 ± 2

The values are mean ± SE.
* Significantly different from awake value ($P < 0.05$).
† Significantly different from Group 1 ($P < 0.05$).
‡ Data from our laboratory (Br J Anaesth 48:545–550, 1976).

humans. In the present study, however, a 17% reduction in CMR_{O_2} was observed at the level of anesthesia characterized by frequent spikes and suppression on the EEG. In the canine studies cerebral metabolic depression with enflurane also was reported, and the reduction in CMR_{O_2} was dose related[15,16] but nonlinear.[17] Therefore, our observation of no significant differences in CMR_{O_2} between group 1 and the awake group may reflect a nonlinear response of cerebral metabolic depression with enflurane.

With surgical stimulation, CMR_{O_2} and CBF remained unchanged, despite the EEG changes. In our laboratory we previously demonstrated in the dog that EEG desynchronization, as produced by electrical stimulation of a peripheral nerve, was accompanied by an increase in CMR_{O_2}.[18] With deepening of anesthesia, CMR_{O_2} remained unchanged, as did the EEG with stimulation during halothane or methoxyflurane anesthesia.[18] This animal study led us to anticipate that the EEG changes in group 2 during surgery might be accompanied by a significant change in CMR_{O_2}. However, this was not the case. This might be due to differences in the area of the brain where the CBF and CMR_{O_2} were measured. Namely, in the canine studies, cerebral hemispheric CBF and CMR_{O_2} were measured, while in humans CBF and CMR_{O_2} of the whole brain were measured. However, unchanged CMR_{O_2} does not necessarily mean unaltered neuronal function. Instead, it is more likely that redistribution of blood flow coupled with metabolic change occurred with surgical stimulation.

The present study showed that the balance between oxygen supply and demand in the whole brain was well maintained during enflurane anesthesia when CPP was maintained above 60 mmHg. Enflurane caused an increase in CBF and a decrease in CMR_{O_2} during surgical depth of anesthesia.

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