

## Cerebral Circulation and Metabolism during Enflurane Anesthesia in Man

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**Abstract** The effects of enflurane anesthesia on cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ( $CMRO_2$ ) were studied in 17 patients. The patients were divided into two groups according to the depth of anesthesia, i.e., group I, 2% inspired enflurane, and group II, 3.5% inspired enflurane. Cerebral perfusion pressure (CPP) was maintained above 60 mmHg with phenylephrine. In group I, patients were studied before surgery, while in group II, the measurements were performed before and during surgery. In group I (enflurane concentration in the arterial blood, 15 mg/dl), mean CBF and  $CMRO_2$  were 53 and 2.8 ml/100g/min, respectively. These values were not significantly different from CBF (46 ml/100g/min) and  $CMRO_2$  (3.1 ml/100g/min) in the awake patients. The electroencephalogram (EEG) showed predominant activities between 12 and 15 Hz with amplitude of 50 to 100  $\mu$ V with anterior dominance. In group II before surgery (enflurane concentration, 27 mg/dl), mean CBF (61 ml/100g/min) and  $CMRO_2$  (2.6 ml/100g/min) were significantly different from the awake values, while the EEG showed frequent spikes and suppression. In group II during surgery (enflurane concentration 27 mg/dl), mean CBF (67 ml/100g/min) and  $CMRO_2$  (2.6 ml/100g/min) were not different from the values before surgery despite significant EEG changes (decreased spiking, increased suppression). The results indicate that enflurane is a cerebral vasodilator and causes an increase in CBF and a decrease in  $CMRO_2$  in man at an anesthetic level characterized by frequent spikes and suppression on the EEG. No changes in CBF and  $CMRO_2$  despite EEG changes with surgical stimulation suggest redistribution of flow coupled with metabolism.

*Key Words:* Anesthetics; enflurane, Brain: blood flow, oxygen consumption, glucose consumption

### Introduction

Enflurane is known to cause muscle twitching and tonic-clonic convulsion with EEG seizure pattern at deep level of anesthesia<sup>1-3</sup>. This stimulating effect which is different from that of other volatile anesthetics must

be evaluated in terms of its impact on the balance between oxygen supply and demand. However, the effects of enflurane on cerebral blood flow (CBF) and oxygen consumption ( $CMRO_2$ ) have not been thoroughly investigated in man. Wollman et al<sup>4</sup> reported that CBF remained unchanged while  $CMRO_2$

decreased by 50% at a level of anesthesia characterized by frequent EEG spike activity separated by periods of electrical silence. If CBF during enflurane anesthesia is unchanged as they reported, this drug is unique since all other volatile anesthetics are known to increase CBF<sup>5</sup>). However, subsequent study from the same laboratory<sup>6</sup>), though it is only an abstract form, revealed that enflurane, 1.1 and 1.6 minimum alveolar concentration (MAC), increased CBF by 37% and 80% from the awake values if blood pressure was supported. Rolly and Van Aken<sup>7</sup>) recently reported significant decreases in regional CBF in frontal and occipital region at 2% inspired enflurane anesthesia. However, in their study patients were premedicated with meperidine and anesthesia was maintained in combination with nitrous oxide, 67%, and hence there may be drug interaction, 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 CMRO<sub>2</sub> in man, and in addition to evaluate the CBF and CMRO<sub>2</sub> responses to surgical stimulation.

## Method

Seventeen patients (male; 4, female; 13) who were undergoing elective surgery were studied. Age of patients ranged from 25 to 58. Preoperative examination revealed no cardiopulmonary or neurological disorders in all patients. Atropine sulfate, 0.5 mg, was given intramuscularly 30 min before induction. Anesthesia was induced with enflurane in oxygen and inspired concentration of enflurane was increased to 4% over 3 to 4 min. Endotracheal intubation was facilitated with intravenous administration of pancuronium bromide, 6 to 8 mg. The patients were divided into two groups; group I (7 patients) was investigated at a "light" level of anesthesia without surgical stimulation, and group II (10 patients) was investigated at a "deep" level of anesthesia before surgery and then the measurements were repeated during surgery. After intubation, enflurane concentration was

changed to either 2% in group I or 3.5% in group II. In all patients ventilation was mechanically controlled to maintain normocapnia and nitrogen was added to adjust the inspired oxygen concentration to 33%. A 21 gauge teflon indwelling catheter was placed in the radial artery and 18 gauge Medicut® catheter was placed in the jugular bulb for blood sampling and pressure measurement. The position of catheter tip was confirmed by roentgenogram. In group I, measurements were made 30 min after starting enflurane inhalation, 2%. Arterial enflurane concentration was  $14.5 \pm 0.8$  mg/dl. In group II, measurements were made 30 min after enflurane inhalation, 3.5%, (before surgery) and then 15 to 30 min after the start of abdominal surgery (during surgery). The arterial concentrations of enflurane in group II before and during surgery were  $27.3 \pm 1.0$  mg/dl and  $27.3 \pm 0.9$  mg/dl, respectively. The rectal temperature was monitored by a calibrated thermistor probe and was kept at  $36.8 \pm 0.2^\circ\text{C}$  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 occipital electroencephalograms (EEG) were monitored and recorded continuously (Nihon Koden, MAF5, Japan). CBF was measured by the Kety-Schmidt technique using nitrous oxide, 15%, as the indicator. After the arterial and jugular bulb venous blood sampling, nitrous oxide was added to the gas mixture and nitrogen concentration was adjusted to maintain constant inspired oxygen concentration at 33%. Simultaneous arterial and jugular bulb venous blood samples were obtained at 1, 2, 3, 4, 5, 7, 9, 12, 15 min after the start of inhalation 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 modification of the Kety-Schmidt method which includes prolongation of 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. 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. PO<sub>2</sub>, PCO<sub>2</sub>, pH were measured with blood gas

analyzer (ABL2, Radiometer, Denmark). Oxygen saturation and hemoglobin concentration were measured with IL Co-oximeter (Model 282, Instrumentation Laboratory, U.S.A.). Blood glucose concentration was measured by an enzymatic method. These values were measured before and at 5, 10, 15 min after the start of nitrous oxide inhalation, and the mean values of the 4 samples were shown in table. Arterial and jugular bulb venous blood concentrations of enflurane were measured by gas chromatography. The values shown in the table were the mean of the 3 samples taken before and 5, 15 min after [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  $CMR_{glucose}$  were calculated as the product of CBF and the oxygen content difference or glucose content difference respectively between the arterial and the jugular bulb blood. Oxygen-glucose index was calculated as suggested by Cohen et al<sup>8</sup>). CPP was maintained above 60 mmHg with infusion of phenylephrine (0.005% solution);  $0.4 \pm 0.1 \mu\text{g/kg/min}$  in group I, and  $1.3 \pm 0.3 \mu\text{g/kg/min}$  and  $0.9 \pm 0.1 \mu\text{g/kg/min}$  in group II before and during surgery, respectively. If CPP fell below 60 mmHg despite phenylephrine infusion or if CPP fluctuated more than 10% of the mean value obtained during inhalation of nitrous oxide, the data were discarded. In group II, in order to quantify the EEG change, the frequency of spikes (greater than 100  $\mu\text{V}$ , less than 1/12 sec duration), sharp waves (greater than 100

$\mu\text{V}$ , 1/12-1/5 sec duration), spike-and-wave complex, and the percentage of time occupied by the periods of suppression (electrical silence 1 sec in duration or longer) were determined during 15 min-period of CBF measurement. The analysis was blinded and visually done.

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

## Results

Physiological parameters in each group are summarized in Table 1, and compared with the awake values previously established in our laboratory<sup>9</sup>). Blood concentration of enflurane was maintained constant during measurements.  $P_{aO_2}$  was maintained above 100 mmHg, and  $P_{aCO_2}$  and pH were within the normal range. The mean rectal temperature in the present study ( $36.8^\circ\text{C}$ ) was  $0.6^\circ\text{C}$  higher than the awake group ( $36.2^\circ\text{C}$ ) in which nasopharyngeal temperature was measured. There was no significant difference in age between the groups.

EEG recordings in group I showed predominant 12-15 Hz activities with amplitude of 50 to 100  $\mu\text{V}$  in 5 of 7 patients, while in the remaining two, 8-10 Hz activities with

**Table 1** Physiological Parameters and Anesthetic Concentration during Enflurane Anesthesia

	n	Enflurane concentration mg/dl	MAP mmHg	$P_{aO_2}$ mmHg	$P_{aCO_2}$ mmHg	pH
Group I	7	A $14.5 \pm 0.8$ V $14.5 \pm 0.7$	$81 \pm 2^*$	$135 \pm 7^*$	$37.8 \pm 1.0$	$7.37 \pm 0.02^*$
Group II (before surgery)	10	A $27.3 \pm 1.0$ V $27.0 \pm 0.8$	$76 \pm 3^*$	$191 \pm 32^*$	$34.9 \pm 0.9$	$7.41 \pm 0.01^*$
Group II (during surgery)	10	A $27.3 \pm 0.9$ V $27.3 \pm 0.8$	$80 \pm 3^*$	$177 \pm 31^*$	$36.5 \pm 0.9$	$7.40 \pm 0.01^*$
Awake §	13	A — — V — —	$95 \pm 4$	$473 \pm 12$	$35.1 \pm 1.1$	$7.45 \pm 0.01$

The values are mean  $\pm$  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),  $FI_{O_2} = 1.0$ .

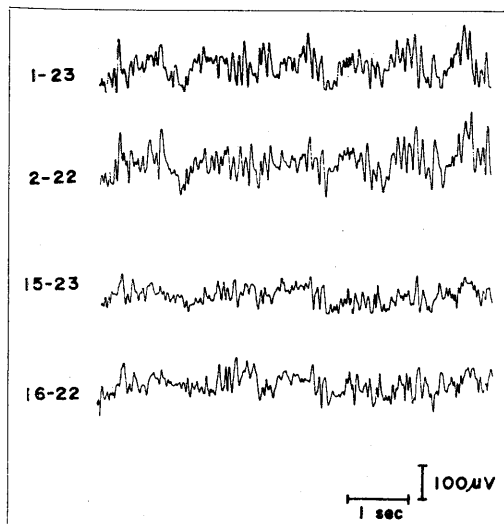


Fig. 1 Representative electroencephalogram during enflurane anesthesia (group I).

Predominant 12 to 15 Hz of 50 to 100  $\mu$ V waves were observed with higher amplitude in frontal leads than in occipital leads (anterior dominance). CBF and  $CMR_{O_2}$  were 56.7 ml/100g/min and 3.0 ml/100g/min, respectively. Enflurane concentration in the arterial blood was 16.8 mg/dl and  $Paco_2$  was 38.5 mmHg.

amplitude of 25 to 50  $\mu$ V were predominant. In all patients anterior dominance<sup>10)</sup> was observed. Representative EEGs in group I and II were shown in Fig. 1 and 2, respectively. Table 2 shows the results of the analysis of EEG in group II. With surgical stimulation, frequencies of spike and spike-and-wave complex were decreased and suppression disappeared in most cases. There was no consistent relationship between individual EEG and  $CMR_{O_2}$  change.

Cerebral circulatory and metabolic parameters are summarized in table 3. Our awake values of CBF and  $CMR_{O_2}$  were  $46 \pm 2$  and  $3.1 \pm 0.2$  ml/100g/min, respectively. CPP was slightly lower in groups I and II as compared with the awake values. There was no significant difference in CBF between group I and the awake group. However the mean

Table 2 Electroencephalographic Changes with Surgical Stimulation during Enflurane Anesthesia (group II)

	Before surgery	During surgery
Spike frequencies/min	$17 \pm 2$	$9 \pm 2^*$
Spike and wave frequencies/min	$4 \pm 1$	$1 \pm 1^*$
Sharp wave frequencies/min	$11 \pm 2$	$13 \pm 2$
Suppression per cent	$10 \pm 2$	$1 \pm 1^*$

The values are mean  $\pm$  SE.

\* Significantly different from the value before surgery ( $P < 0.05$ ).

CBF in group II before surgery was 33% higher than that of the awake group. In group II, the mean CBF during surgery was higher than that of before surgery but the difference did not reach to statistical significance. The mean CVR decrease significantly in groups I and II as compared with the awake values.

There was no significant difference in  $CMR_{O_2}$  between group I and awake group. However, the mean  $CMR_{O_2}$  in group II before surgery was 17% less ( $P < 0.05$ ) than that of awake group. Surgical stimulation did not cause significant change in  $CMR_{O_2}$  as compared with the values before surgery.

The mean  $CMR_{glucose}$  tended to decrease in both group I and II as compared with the awake values. There was no significant decrease in oxygen-glucose index in any group. Jugular venous  $Po_2$  was unchanged in group I and significantly higher in group II than in the awake group.

## Discussion

The present study demonstrates that in man, enflurane causes an increase in CBF (when CPP maintained above 60 mmHg) at a level of anesthesia characterized by frequent spikes and suppression on the EEG. The

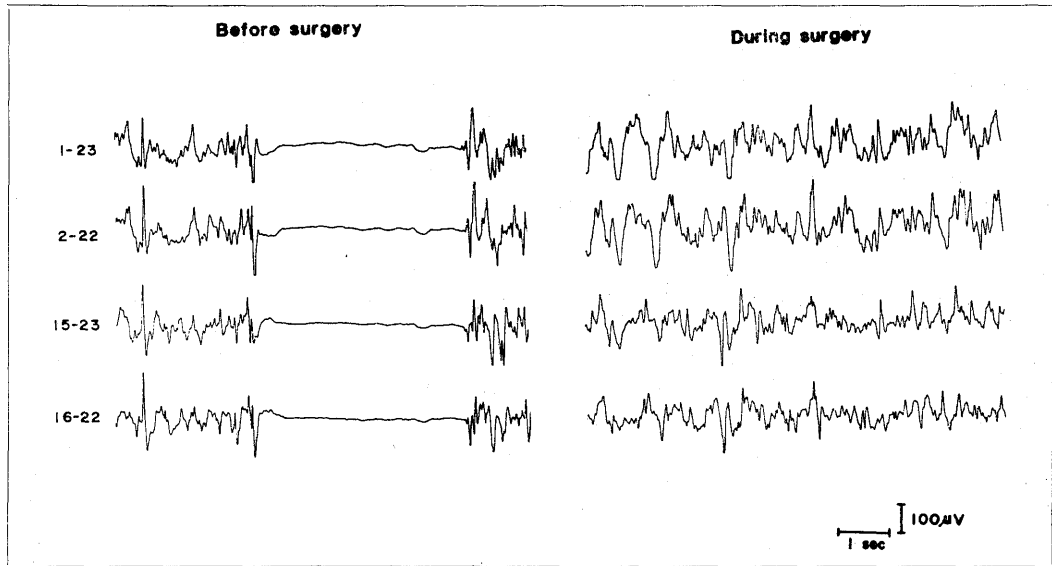


Fig. 2 Representative electroencephalogram during enflurane anesthesia (group II).

Frequent spikes and suppression observed before surgery (left) disappeared during surgery (right). CBF and  $CMR_{O_2}$  before and during surgery were 60 ml/100g/min vs. 72 ml/100g/min and 2.6 ml/100g/min vs. 2.4 ml/100g/min, respectively. Enflurane concentration and  $Paco_2$  before and during surgery were 26.5 mg/dl vs. 25.8 mg/dl and 33.6 mmHg vs. 35.5 mmHg, respectively.

Table 3 Cerebral Circulation and Metabolism during Enflurane Anesthesia

	n	CPP mmHg	CBF ml/100g /min	$CMR_{O_2}$ ml/100g /min	CVR mmHg/ml /100g/min	$CMR_{glucose}$ mg/100g /min	Oxygen- glucose index	Jugular venous $PO_2$
Group I	7	73±2*	53±3	2.8±0.1	1.4±0.1*	4.2±0.6	100±13	42±1
Group II (before surgery)	10	66±3*	61±4*	2.6±0.1*	1.1±0.1*	3.9±0.4	96±9	48±2*
Group II (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 I ( $P<0.05$ ).

‡ Data from our laboratory (Br J Anaesth 48:545-550, 1976).

increase in CBF was accompanied by a reduction in CVR, indicating that enflurane is a cerebral vasodilator. In group I ("light" anesthesia), the significant reduction in CVR could be largely due to a decrease in CPP. Wollman et al<sup>4</sup>) reported no significant ch-

ange in CBF in volunteers during enflurane anesthesia when EEG showed frequent spikes separated by periods of electrical silence. Subsequent study from the same laboratory by Murphy et al<sup>6</sup>) demonstrated that CBF did not change significantly at 0.6 MAC

enflurane but increased by 37 and 80% at 1.1 and 1.6 MAC with arterial blood pressure support, respectively, as compared with the awake values. For comparison, MACs in group I and II in the present study calculated from arterial blood concentration of enflurane, assuming blood gas partition coefficient of 1.91 and MAC of enflurane 1.68%, were 0.6 and 1.2, respectively. However, actual MAC values must be slightly higher because there are several factors which contribute to the difference in the estimation of arterial and end-tidal anesthetic concentration<sup>11</sup>. Then, the anesthetic level may be comparable with that reported by Murphy et al<sup>6</sup>) and therefore, the increase in CBF with arterial blood pressure support observed in this study is in agreement with their results.

Decrease in regional CBF in 2/10 areas, measured by <sup>133</sup>Xe clearance technique, at enflurane, 2%, has been reported by Rolly and Van Aken<sup>7</sup>). This could be the result of combined effects of enflurane, nitrous oxide and meperidine and/or a decrease in MAP to approximately 60 mmHg. The difference between their study and this study, can not be attributable to regional difference because most of the regional CBF values they measured were reduced from control values. The present findings, therefore, suggest that enflurane at "deep" level of anesthesia causes an increase in CBF when CPP is maintained above the lower limit of CBF autoregulation.

Studies in the dog indicated that hemispheric CBF was either increased or unchanged with enflurane<sup>12,13</sup>). This difference also could be explained by the fact that the reduction in CPP was greater in the report where CBF did not increase<sup>13</sup>). From these considerations, the author concludes that the effect of anesthetics on CBF must be evaluated when CPP is maintained. Wollman et al<sup>4</sup>) found 50% reduction in CMRO<sub>2</sub> with enflurane anesthesia while EEG showed frequent spikes and suppression. This is the

largest decrease ever reported in volatile anesthetics. However, Murphy et al<sup>6</sup>) from the same laboratory reported, subsequently, that CMRO<sub>2</sub> was unchanged or slightly decreased during enflurane anesthesia (0.6 to 1.6 MAC), though, they did not present the actual values. There seems, therefore, to be discrepancies between their two studies and it is difficult to compare the cerebral metabolic effects of enflurane reported in their studies with the present study. In this study, however, 17% reduction in CMRO<sub>2</sub>, as compared with the awake value, was observed at a "deep" level of anesthesia. Cerebral metabolic depression with enflurane was also reported in the canine studies and the reduction in CMRO<sub>2</sub> seems to be dose-related<sup>12-14</sup>) but nonlinear<sup>14</sup>). Therefore, no significant changes between group I and awake group may reflect nonlinear response of cerebral metabolic depression with enflurane.

With surgical stimulation, CMRO<sub>2</sub> and CBF remained unchanged despite the apparent EEG changes. In our laboratory it was demonstrated in the dog that EEG desynchronization produced by electrical stimulation during the peripheral nerve was accompanied by an increase in CMRO<sub>2</sub>, but with deepening of anesthesia CMRO<sub>2</sub> remained unchanged when EEG did not change with stimulation during halothane or methoxyflurane anesthesia<sup>15</sup>). This animal study led us to anticipate that EEG change in group II during surgery might be accompanied by a significant change in CMRO<sub>2</sub>. However, this was not a case in the present study. This might be due to the difference of the area of the brain where the CBF and CMRO<sub>2</sub> were measured. Namely, in the canine studies cerebral hemispheric CBF and CMRO<sub>2</sub> were measured while in man CBF and CMRO<sub>2</sub> of a whole brain were measured. However, unchanged CMRO<sub>2</sub> does not necessarily mean unaltered neuronal function. Instead, it is more likely that the redistribution of blood flow coupled with metabolic change occurred with surgical sti-

mulation.

The present study shows that the balance between oxygen supply and demand in a whole brain was well maintained during enflurane anesthesia when CPP was maintained above 60 mmHg as judged by oxygen-glucose index and by jugular venous  $P_{O_2}$ . In summary enflurane caused an increase in CBF and a decrease in  $CMR_{O_2}$  and there was no metabolic derangement during surgical depth of anesthesia.

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## References

- 1) Virtue, R.W., Lund, L.O., Phelps, M. Jr., Vogel, J.H.K., Beckwith, H., Heron, M.: Difluoromethyl 1, 1, 2-trifluoro-2-chloroethyl ether as an anaesthetic agents: Results with dogs, and a preliminary note on observations with man. *Can. Anaesth. Soc. J.*, 13 : 233-241, 1966.
- 2) Neigh, J.L., Garman, J.K., Harp, J.R.: The electroencephalographic pattern during anesthesia with Éthrane: Effects of depth of anesthesia,  $P_{aCO_2}$ , and nitrous oxide. *Anesthesiology*, 35 : 482-487, 1971.
- 3) Lebowitz, M.H., Blitt, C.D., Dillon, J.B.: Enflurane-induced central nervous system excitation and its relation to carbon dioxide tension. *Anesth. Analg.*, 51 : 355-363, 1972.
- 4) Wollman, H., Smith, A.L., Neigh, J.L., Hoffman, J.C.: Cerebral blood flow and oxygen consumption in man during electroencephalographic seizure patterns associated with Éthrane anesthesia. *Cerebral Blood Flow*. Edited by Brock M, Fieschi C, Ingver DH et al. Springer-Verlag, Berlin, 1969, pp. 246-248.
- 5) Lassen, N., Shapiro, H.M.: Anaesthesia and cerebral blood flow. *A Basis and Practice of Neuroanesthesia*. Edited by Gordon E. Excerpta Medica, Amsterdam 1981, pp. 139-172.
- 6) Murphy, F.L., Kennell, E.M., Johnstone, R.E., Lief, P.L., Joves, D.R., Tompkins, B.M., Gutsche, B.B., Behar, M.G., Wollman, H.: The effects of enflurane, isoflurane, and halothane on cerebral blood flow and metabolism in man. Abstracts of Scientific Paper, American Society of Anesthesiologists Annual Meeting. p. 61, 1974.
- 7) Rolly, G., Van Aken, J.: Influence of enflurane on cerebral blood flow in man. *Acta Anaesth. Scand.*, Suppl 71 : 59-63, 1979.
- 8) Cohan, P.J., Alexander, S.C., Smith, T.C., Reivich, M., Wollman, H.: Effects of hypoxia and normocarbica on cerebral blood flow and metabolism in conscious man. *J. Appl. Physiol.*, 23 : 183-189, 1967.
- 9) Sari, A., Maekawa, T., Tohjo, M., Okuda, Y., Takeshita, H.: Effects of althesin on cerebral blood flow and oxygen consumption in man. *Br. J. Anaesth.*, 48 : 545-550, 1976.
- 10) Tinker, J.H., Sharbrough, F.N., Michenfelder, J.D.: Anterior shift of the dominant EEG rhythm during anesthesia in the Java monkey: Correlation with anesthetic potency. *Anesthesiology*, 46 : 252-259, 1977.
- 11) Eger, E. I. II., Bahlman, S.H.: Is the end-tidal anesthetic partial pressure an accurate measure of the arterial anesthetic partial pressure? *Anesthesiology*, 35 : 301-303, 1971.
- 12) Michenfelder, J.D., Cucchiara, R.F.: Canine cerebral oxygen consumption during enflurane anesthesia and its modification during induced seizures. *Anesthesiology*, 40 : 575-580, 1974.
- 13) Sakabe, T.: Effect of enflurane (Éthrane) on canine cerebral metabolism and circulation. *Jpn. J. Anesthesiol.* 24 : 323-331, 1975.
- 14) Stullken, E.H., Milde, J.H., Michenfelder, J.D., Tinker, J.H.: The nonlinear responses of cerebral metabolism to low concentrations of halothane, enflurane, isoflurane, and thiopental. *Anesthesiology*, 46 : 28-34, 1977.
- 15) Kuramoto, T., Oshita, S., Takeshita, H., Ishikawa, T.: Modification of the relationship between cerebral metabolism, blood flow, and electroencephalogram by stimulation during anesthesia in the dog. *Anesthesiology*, 51 : 211-217, 1979.