Relationship between the Cerebral Metabolism, Blood Flow and Electroencephalogram during Anesthesia in the Dog

Shuzo OSHITA
Department of Anesthesiology, Yamaguchi University School of Medicine Ube, Yamaguchi, Japan
(Received June 14, 1979)

ABSTRACT

The effects of sciatic nerve stimulation on the cerebral metabolic rate for oxygen ($CMRo_2$), cerebral blood flow (CBF) and electroencephalogram (EEG) were investigated in anesthetized dogs. With 0.12 and 0.25 per cent methoxyflurane, the $CMRo_2$ increased by 10 and 13 per cent, being accompanied by EEG activation, and the CBF increased by 8 and 17 per cent, respectively. With 0.38 per cent methoxyflurane, the $CMRo_2$ and EEG remained unchanged, but the CBF increased by 8 per cent. With 0.5 and 1.5 mg/kg morphine, the $CMRo_2$ increased by 13 and 12 per cent, being accompanied by EEG activation, and the CBF increased by 15 and 11 per cent, respectively. Addition of 60 per cent nitrous oxide to 1.5 mg/kg morphine increased the $CMRo_2$, being accompanied by EEG activation, and CBF by 12 and 24 per cent, respectively. These results suggest that the coupling of $CMRo_2$ and EEG was maintained in all anesthetic circumstances but the coupling of $CMRo_2$ and CBF was lost with 0.38 per cent methoxyflurane and morphine-nitrous oxide anesthesia.

Key Words: *cerebral metabolism*; *blood flow*; *EEG*; *anesthetic*

INTRODUCTION

Although the coupling between the cerebral metabolism, blood flow and function was extensively studied in both normal subjects[1] and the patients with cerebral disease[2], the coupling during anesthesia had been remained obscure until it was studied by Kuramoto[3] in our laboratory. He studied the modification of the relationship between the cerebral metabolic rate for oxygen ($CMRo_2$), blood flow (CBF) and electroencephalogram (EEG) by the stimulation of sciatic nerve and suggested that the relationship would be varied with different anesthetics and anesthetic

levels. His suggestion that cerebral vasodilator such as halothane is capable to produce a significant increase in CBF without any increase in $CMRo_2$ or EEG activation lead the author to examine the effects of anesthetics, which have different actions on cerebral metabolism and circulation, on the relationship. Accordingly, in this study the modification of the relationship between the $CMRo_2$, CBF and EEG by sciatic nerve stimulation was examined during methoxyflurane, morphine or morphine-nitrous oxide anesthesia in the dog.

MATERIALS and METHODS

The effect of sciatic nerve stimulation on the $CMRo_2$, CBF and EEG was determined in fourteen unpremedicated mongrel dogs (weighing 12 to 18 kg) during anesthesia with methoxyflurane, morphine and morphine-nitrous oxide.

Anesthesia was induced with halothane in oxygen. Then succinylcholine was given to facilitate tracheal intubation and thereafter gallamine was administered at 50 mg per hour to maintain muscle paralysis. During the surgery, halothane was administered to the dogs at the concentration of 1.0 to 1.5 per cent in a gas mixture of 60 per cent nitrogen and 40 per cent oxygen. After the completion of the surgery, inspired halothane concentration was reduced to a level of 0.2 per cent and then at least 1 hour was elapsed before the start of experiment. Dogs were then divided into two different groups: methoxyflurane (6 dogs); and morphine (8 dogs, 60 per cent nitrous oxide was added to 5 dogs among them). In the methoxyflurane group 0.12 per cent methoxyflurane was initially administered. At this level of anesthesia, control measurements were obtained over a 10 to 15-minute period and mean values were calculated from 5 to 8 consecutive determinations of CBF and $CMRo_2$. Following control measurements, the stimulation of both sciatic nerves was applied with supramaximal rectangular stimuli (6 volts, 0.1 msec, 100 Hz). During the stimulation, arterial and sagittal sinus blood were sampled at 1 minute intervals. Methoxyflurane concentration was then increased to 0.25 and 0.38 per cent in a stepwise manner, control measurements starting at least 30 minutes after the change of inspired concentration. Two to three minutes after the completion of control measurements the sciatic nerves were stimulated. In the morphine group, control measurements were began 30 minutes after 0.5 mg/kg of morphine was administered and followed closely by measurements during stimulation. Thirty minutes later, an additional 1.0 mg/kg of morphine was given, resulting in total accumulated doses of 1.5 mg/kg. Thirty minutes after the additional morphine, the measure-

ment was started. Morphine was administered intravenously at a rate of 0.2 mg/kg/min. Thirty minutes after the end of stimulation during 1.5 mg/kg of morphine, nitrogen (60 per cent) was substituted for nitrous oxide (60 per cent) in 5 of the 8 dogs. Measurements commenced 30 minutes later. The end-tidal concentration of methoxyflurane and nitrous oxide was frequently analyzed by gaschromatography (Shimazu GC-4).

In both groups, the surgical preparation originally described by Michenfelder et al[4]. was used for CBF measurements. In this method, cannulation of the sagittal sinus was performed and sagittal sinus blood was diverted and returned to the left external jugular or mandibular vein. Both femoral arteries were cannulated for blood sampling and pressure measurements, and both femoral veins were cannulated for the infusion of blood, lactated Ringer's solution and drugs. Both sciatic nerves were carefully exposed and cut at the thigh level. This proximal ends were then gently placed on the bipolar silver-silver chloride electrodes which were separated 1 cm from each other. Sciatic nerve temperature was maintained by warmed liquid paraffin around the exposed area. After the completion of the surgical preparation, lidocaine (5 mg/kg, 0.5 per cent solution) was infiltrated into the skin and muscle of the head and in the area where the catheters were placed. Additional lidocaine (half of the initial dose) was given hourly.

CBF was measured by the electromagnetic flowmeter (Nihon Kohden ,MF-46). The flowmeter probe with a lumen diameter of 3 mm was placed around the cannula, draining the sagittal sinus blood, and 1 cm away from the draining portion of the sinus. To insure exact measurement, the electromagnetic flowmeter incorporated a nonocclusive zero and a 3.0-sec time constant. In addition, the flowmeter was frequently calibrated by direct timed measurement of the sagittal sinus blood flow, and the zero-flow reference was established at about 1 hour intervals by occluding the drainage cannula on both sides of the probe. The percentage of drained brain and the individual brain weights of the dogs studied were used to convert units of flow from milliliters per minute to milliliters per 100 g of brain per minute.

Oxygen content of the arterial or sagittal sinus blood was calculated from measurements of oxyhemoglobin (IL 182, Co-oximeter) and oxygen tension (IL 313 electrode). pH and $Paco_2$ were measured with appropriate electrodes. The $CMRo_2$ was calculated as the product of CBF and the difference in oxygen content of the arterial and sagittal sinus blood. Cerebral vascular resistance (CVR) was calculated as the ratio of mean arterial blood pressure (MAP) to CBF. The EEG was continuously

monitored using parietal bipolar silver-silver chloride electrodes.

Ventilation and F_{IO_2} were adjusted to maintain $Paco_2$ at 35 ± 0.4 torr and Pao_2 at 195 ± 3 torr. Sodium bicarbonate was given as needed to keep the buffer base normal. Epidural temperature, hemoglobin level were maintained at $37.5\pm0.1°C$ and 13 ± 0.1 g/dl, respectively. MAP during the control measurement was maintained above 80 torr in all dogs. In order to maintain this pressure level, phenylephrine, which is reported to have no effect on cerebral metabolism and circulation[5], was administered, only when MAP decreases below 80 torr occured with deepening of anesthesia despite appropriate blood replacement.

At the end of the experiment it was confirmed that the autoregulation of the CBF from 50 to 150 torr (using induced hemorrhage and phenylephrine infusion) was intact and that the CBF increased appropriately in response to the addition of 5 to 15 per cent CO_2.

At autopsy, the absence of extracerebral venous connections to the sagittal sinus were confirmed by injecting vinyl acetate and the brain was removed and weighed.

All the data were subjected to analysis of variance. Statistical difference of $P<0.05$ was considered to be significant.

RESULTS

Pertinent summaries are in Table 1 and 2. Representative EEG patterns are shown in Fig. 1. The time course of the per cent control of $CMRo_2$ and CBF are shown in Fig. 2.

Methoxyflurane:

At 0.12 per cent the $CMRo_2$ and CBF peaked at 1 minute, thereafter, returning to the control level. The mean increase in $CMRo_2$ and CBF was 10 and 8 per cent, respectively. The EEG was initially activated by stimulation and returned to the control pattern toward the end of stimulation.

At 0.25 per cent, the mean $CMRo_2$ and CBF increased by 13 and 17 per cent during the stimulation, respectively. The EEG was moderately activated by the stimulation and gradually returned to the control pattern.

At 0.38 per cent, neither the $CMRo_2$ nor the EEG displayed significant changes throughout the stimulation. The CBF increased significantly (13 per cent during the first two minutes), displaying a mean increasing of 8 per cent during stimulation.

Morphine:

At 0.5 mg/kg, the mean $CMRo_2$ and CBF increased by 13 and 15 per cent during stimulation, respectively. The EEG was initially activat-

Table 1 Effects of sciatic nerve stimulation on cerebral metabolism and circulation during methoxyflurane anesthesia

Methoxyflurane concentration	Time during stimulation (min)	$CMRo_2$ (ml/100g/min)		MAP (torr)		CBF (ml/100g/min)		CVR (torr/ml/100g/min)	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE
0.12 per cent	Control	5.63	0.11	102	6	47	2	2.20	0.14
	1	6.53*	0.26	122	11	58*	2	2.13	0.21
	2	6.23*	0.17	118	12	52*	1	2.23	0.24
	3	6.18*	0.24	115	12	50	1	2.28	0.25
	4	6.15*	0.18	112	14	48	2	2.27	0.25
	5	5.76	0.11	103	9	47	2	2.16	0.19
0.25 per cent	Contro	4.82	0.23	95	5	47	5	2.16	0.32
	1	5.48*	0.31	100	6	59*	8	1.81*	0.26
	2	5.50*	0.21	97	7	56*	7	1.86	0.26
	3	5.48*	0.26	94	7	55*	6	1.89	0.24
	4	5.35	0.20	90	6	53	6	1.81	0.23
	5	5.34	0.23	89	5	53	7	1.85	0.28
0.38 per cent	Control	4.32	0.14	94	3	48	5	2.09	0.27
	1	4.64	0.23	86	3	55*	6	1.66*	0.21
	2	4.62	0.21	86	4	53*	7	1.75*	0.25
	3	4.57	0.23	84	6	52	6	1.79*	0.26
	4	4.42	0.18	85	6	51	6	1.82*	0.26
	5	4.24	0.15	87	5	50	6	1.89*	0.25

*Significantly different from control ($P<0.05$)

ed, thereafter displaying little tendency to return to the control pattern.

At 1.5 mg/kg, the mean $CMRo_2$ and CBF increased by 12 and 11 per cent during the stimulation. The change in EEG induced by stimulation was very similar to that of 0.5 mg/kg morphine.

With 1.5 mg/kg plus nitrous oxide (60 per cent), the $CMRo_2$ and CBF during stimulation increased by 12 and 24 per cent, respectively. The control EEG was of lower voltage than that of the previous two dose levels of morphine. Upon stimulation, the EEG was initially activated then gradually returned to near the control pattern.

DISCUSSION

The present study indicates the tight coupling between the $CMRo_2$ (as a reflection of metabolism) and EEG (as a reflection of function) during methoxyflurane, morphine and morphine-nitrous oxide anesthesia. EEG activation by sciatic nerve stimulation was consistently accompanied by an increase in $CMRo_2$ and, furthermore, the individual time course

Table 2 Effects of sciatic nerve stimulation on cerebral metabolism and circulation during morphine and morphine-nitrous oxide anesthesia.

Morphine doses	Time during stimulation (min)	$CMRo_2$ (ml/100g/min)		MAP (torr)		CBF (ml/100g/min)		CVR (torr/ml/100g/min)	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE
0.5 mg/kg	Control	4.71	0.25	110	7	48	4	2.38	0.21
	1	5.40*	0.27	130*	13	60*	5	2.26	0.24
	2	5.42*	0.29	129*	11	57*	5	2.37	0.23
	3	5.40*	0.28	125*	10	55*	5	2.40	0.23
	4	5.24*	0.24	122	9	53*	4	2.39	0.23
	5	5.12*	0.34	121	9	52	5	2.46	0.25
1.5 mg/kg	Control	4.56	0.32	107	6	48	4	2.35	0.26
	1	5.38*	0.31	140*	9	58*	4	2.50	0.23
	2	5.18*	0.32	136*	8	55*	4	2.59	0.25
	3	5.06*	0.32	129*	8	53*	4	2.55	0.24
	4	4.98*	0.35	125*	9	51	4	2.54	0.26
	5	4.84	0.30	117	11	50	4	2.45	0.27
1.5 mg/kg + N_2O 60 per cent	Control	5.38	0.57	100	3	54	7	1.97	0.24
	1	6.43*	0.67	120	11	75*	9	1.75	0.32
	2	5.97*	0.67	117	10	67*	8	1.89	0.31
	3	5.92	0.74	110	9	66*	9	1.82	0.29
	4	5.87	0.69	108	8	65*	8	1.79	0.27
	5	5.82	0.65	106	8	63*	9	1.81	0.29

*Significantly different from control ($P<0.05$)

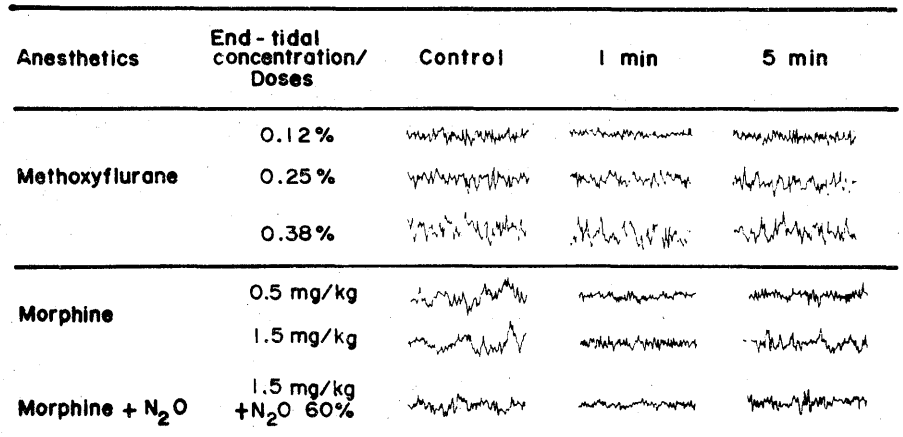

Fig 1 Representative EEG patterns, taken at 1 and 5 minutes, respectively, after the start of stimulation, at different end-tidal concentrations or doses of anesthetics.

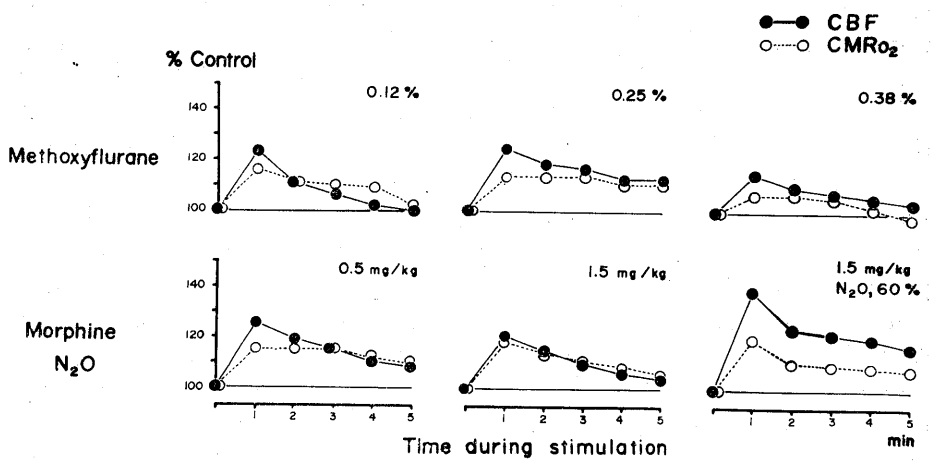

Fig 2. The time course of the per cent control of $CMRo_2$ and CBF at different end-tidal concentrations or doses of anesthetics.

of the changes in the $CMRo_2$ was closely related to that of the EEG pattern in all anesthetic circumstances. However, with 0.38 per cent methoxyflurane, there was a significant increase in CBF without any change in $CMRo_2$ and EEG. In addition, with 1.5 mg/kg morphine-60 per cent nitrous oxide, the response of CBF to the stimulation was over twice that of 1.5 mg/kg morphine alone, despite almost the same increase in the $CMRo_2$ in both conditions. Thus, in all anesthetic conditions there was a tight coupling between cerebral metabolism and function, but not between metabolism and blood flow. Kuramoto[3] studied the effects of sciatic nerve stimulation on the $CMRo_2$, CBF and EEG during halothane anesthesia in the dog. In his study the $CMRo_2$ and CBF increased significantly and the EEG was apparently activated at the end-tidal halothane concentration of 0.2, 0.5 and 0.9 per cent, but with 1.4 per cent halothane the $CMRo_2$ and the EEG remained unchanged from control in spite of significant increase of CBF. From these results, he concluded that the coupling of $CMRo_2$ and EEG was maintained at all anesthetic levels of halothane but that the coupling of $CMRo_2$ and CBF was variable with different levels of anesthesia. In the comparison between the results of our study and those of Kuramoto's study, the magnitude of an increase in CBF with 0.38 per cent methoxyflurane, which is equivalent to 1.4 per cent halothane as judged minimal alveolar concentration[6], was less than that observed with 1.4 per cent halothane. During morphine-nitrous oxide anesthesia there was striking increase in CBF, which was comparable with 1.4 per cent halothane, as a response

to stimulation. These differences at the responses of CBF to the stimulation in the different anesthetics may be explained by the different effects of each anesthetics on the CBF. Michenfelder[7] studied the effect of methoxyflurane on CBF and concluded that it resembles halothane in its cerebral metabolic effects but, unlike halothane, produces only modest changes in CBF. Takeshita[8] also reported that methoxyflurane did not cause significant CBF increase in the dog. However, in both reports there was considerable decrease in mean arterial blood pressure (MAP) and made it difficult to exclude the autoregulatory compensation of CBF. In this study MAP was carefully maintained at well above the autoregulatory range. Nitrous oxide produces significant increase in CBF. Sakabe et al[9]. found that 60 per cent nitrous oxide, in combination with 0.2 per cent halothane, increases CBF to a maximum of 203 per cent of control. On the other hand morphine is known to reduce CBF. Takeshita and Michenfelder[10] reported 55 per cent decrease in CBF with 1.2 mg/kg morphine in the dog.

The results also reconfirm a progressive decrease in the level of $CMRo_2$ with increasing concentrations of methoxyflurane. We had anticipated a decrease in the per cent change in $CMRo_2$ in response to stimulation as anesthesia deepened, but the peak and average increase in $CMRo_2$ were similar in the two lowest levels of methoxyflurane. These results suggest that there may be a threshould effect in terms of evoked metabolic and EEG responses with the onset of the anesthetic state on the methoxyflurane as seen with halothane in Kuramoto's study[3].

Recent studies have emphasized that regional changes in CBF are related to the functional state of the awake brain. It was shown by Raichle[11] that an increase in regional CBF was accompanied by an increase in regional $CMRo_2$ in conscious man. Ingvar and his colleagues [2] also found a close relationship between changes in the mean hemispheric $CMRo_2$ and those in the regional CBF in chronic, mainly psychiatric, patients. Results of the present study, indicate that during 0.38 per cent methoxyflurane and morphine-nitrous oxide anesthesia there is a poor correlation, at least quantitatively, between CBF and cortical activities as reflected by EEG and $CMRo_2$.

The increase in CBF during 0.38 per cent methoxyflurane must depend upon vasodilation because the MAP was little affected. If we accept the theory that cerebral vasodilation occurs in response to demand for oxygen during increased neuronal activities, then our results during methoxyflurane (0.12 and 0.25 per cent) and in morphine anesthesia may be explained by this view. However, this hypothesis does not explain all situations in the present study because the CBF unpro-

portionately increased in 1.5 mg/kg morphine-60 per cent nitrous oxide. Therefore the present study suggests that the uncoupling between $CMRo_2$ and CBF could be related to the cerebral vascular effects of individual anesthetics. It has been known that inhalational anesthetics, capable to dilate cerebral vessels, increase the sensitivity of cerebral vessels to an increase in $Paco_2$[12]. The metabolic regulation of the CBF was such that when the brain performs work, more energy is used for ion-pumping and transmitter synthesis, more energy is produced by oxidative glucose combustion and more energy is supplied by an increase in blood flow[13]. Therefore, if the brain tissue CO_2 increase with metabolic enhancement, being accompanied by EEG activation, due to stimulation there might be more pronounced cerebral vasodilatation with potent cerebral vasodilator such as halothane or nitrous oxide. On the contrary, it can be considered that the brain tissue CO_2 does not increase significantly in such a case that neither the $CMRo_2$ nor the EEG display significant changes. If it is true, the prominent increase of CBF without any change in $CMRo_2$ and EEG, observed at 1.4 per cent halothane in Kuramoto's study[3], can not be explained by the metabolic theory.

Langfitt and Kassell[14] reported that the stimulation of the brain stem invariably altered the EEG pattern and produced an increase in CBF without a change in blood pressure in five cord-sectioned monkeys anesthetized with pentobarbital sodium. They concluded that the most likely explanation for the cerebral vasodilatation was the neurogenic mechanism because of the very short time between stimulation and response. In our study, the latent time before the CBF increase was but a few seconds in all anesthetic circumstances. Therefore, an alternative explanation of the remarkable change in CBF during morphine-nitrous oxide anesthesia may be neurogenic mechanism whose reaction was enhanced by nitrous oxide. However, there has been no supporting evidence for a neuronal vasomotor mechanism which would explain our results. Thus, any of the presently available data would not be satisfactory to explain the present result and the nature of cerebral vasodilatation produced by anesthetics awaits further study.

In conclusion, the coupling of $CMRo_2$ and EEG was maintained in all tested anesthetic circumstances, but the coupling of $CMRo_2$ and CBF varied with individual anesthetics. It was suggested that cerebral vasodilator may cause more pronounced uncoupling of $CMRo_2$ and CBF, and this fact would be explained by the metabolic theory for CBF regulations.

The author greatfully acknowledgs the suggestion and encouragement of Prof. H. Takeshita, Department of Anesthesiology.

(This work is a thesis of Graduate School of Medicine, Yamaguchi University)

REFERENCES

1) Olesen, J.: Contralateral focal increase of cerebral blood flow in man during arm work. *Brain*, 94 : 635-646, 1971.
2) Ingvar, D.H., Sjolund, B. and Ardo, A.: Correlation between dominant EEG frequency, cerebral oxygen uptake and blood flow. *Electroencephalogr. Clin. Neurophysiol.*, 41 : 268-276, 1976.
3) Kuramoto, T.: Modification of the relationship between the electroencephalogram, cerebral metabolism and blood flow by stimulation during halothane anesthesia in the dog. *Bull. Yamaguchi Med. Sch.*, 24, 205-215, 1977.
4) Michenfelder, J. D., Messich, J. M. and Theye, R. A.: Simultaneous cerebral blood flow measured by direct and indirect methods. *J. Surg. Res.*, 8 : 475-481, 1968.
5) Smith, A.L., Neigh, J.L., Hoffman, J.C. and Wollman, H.: Effects of general anesthesia on autoregulation of cerebral blood flow in man. *J. Appl. Physiol.*, 29 : 665-669, 1970.
6) Eger, E.I. II., Saidman, L.J. and Brandstater, B.: Minimum alveolar anesthetic concentration: A standard of anesthetic potency. *Anesthesiology*, 26 : 756-763, 1965.
7) Michenfelder, J.D. and Theye, R.A.: Effects of methoxyflurane on canine cerebral metabolism and blood flow. *Anesthesiology*, 38 : 123-127, 1973.
8) Takeshita, H., Ishikawa, T. and Okuda, Y.: The effects of methoxyflurane on canine cerebral oxygen consumption and circulation (in Japanese). *Jpn. J. Anesthesiol.*, 18 : 298-303, 1973.
9) Sakabe, T., Kuramoto, T., Inoue, S. and Takeshita, H.: Cerebral effects of nitrous oxide in the dog. *Anesthesiology*, 48 : 195-200, 1978.
10) Takeshita, H., Michenfelder, J.D. and Theye, R.A.: The effects of morphine and N-allylnormorphine on canine cerebral metabolism and circulation. *Anesthesiology*, 37 : 605-612, 1972.
11) Raichle, M.: Sensori-motor area increase of oxygen uptake and blood flow in the human brain during contralateral hand exercise; Preliminary observations by the 0-15 method. *In* D.H. Ingvar and N.A. Lassen (eds.), *Brain Work, The Coupling of Function, Metabolism and Blood Flow in the Brain*, Munksgaard, Copenhagen, 1975, pp. 372-376.
12) Christensen, M.S., Hedt-Rasmussen, K. and Lassen, N.A.: Cerebral vasodilatation by halothane anesthesia in man and its potentiation by hypotension and hypercapnia. *Brit. J. Anaesth.*, 39 : 927-934, 1967.
13) Lassen, N.A. and Christensen, M.S.: Physiology of cerebral blood flow. *Br. J. Anaesth.*, 48 : 719-734, 1976.
14) Langfitt, T.W. and Kassell, N.F.: Cerebral vasodilatation produced by brain-stem stimulation : neurogenic control vs. autoregulation. *Am. J. Physiol.*, 215 : 90-97, 1968.