Cerebral Effects of Nitrous Oxide

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SUMMARY

The cerebral effects of 60 per cent (end-tidal concentration) nitrous oxide (N_2O) were examined in 29 dogs. With the inhalation of N_2O, the cerebral blood flow (CBF) increased, reaching a peak of 203 per cent of the control value at 7 minutes, and thereafter decreased gradually to 125 per cent of the control over a 60 minute-period. The mean cerebral metabolic rate for oxygen ($CMRo_2$) increased to about 120 per cent of the control value within 15 minutes and remained elevated during the inhalation of N_2O. There was no significant change in the mean arterial pressure (MAP), but a significant reduction in cerebral vascular resistance (CVR) was observed. The electroencephalogram (EEG) showed low voltage, slow wave activity with the inhalation of N_2O. After the intravenous injection of thiamylal (8 mg/kg), N_2O increased neither the CBF nor $CMRo_2$ for the first 30 minute-period, but produced predominant slow wave activity during the period. Pretreatment with reserpine (total 1.0 mg/kg) did not modify significantly the cerebral circulatory, metabolic and electrographic effects of N_2O. The cerebral responses to the alteration in $Paco_2$ did not differ significantly during increased metabolism with N_2O from the control without N_2O. In conclusion, N_2O is a cerebral metabolic stimulant which accompanies the increase in the CBF, and EEG slowing. The cerebral circulatory and metabolic stimulation was blocked by prior administration of thiamylal but not by pretreatment with reserpine.

INTRODUCTION

Previous studies on cerebral circulation[1], metabolism[2] and electrical activity[3],[4] of the brain during anesthesia have independently contributed to the elucidation of the mechanism of anesthesia at the central nervous system. However, there have been few investigations covering these three areas. The purpose of this paper is to examine the cerebral effects of N_2O from the circulatory, metabolic and electrographic stand-

points. Wollman and his associates[5] reported a 23 per cent decrease in the cerebral metabolic rate for oxygen ($CMRo_2$) and no change in the cerebral blood flow (CBF) in human volunteers anesthetized with 70 per cent N_2O. On the other hand, Theye and Michenfelder[6] observed a 11 per cent increase in the $CMRo_2$, which was accompanied by an increase in the CBF in dogs. Clark and Rosner[3,4] described in their review the electroencephalographic changes with N_2O. Progressive loss of alpha rhythm started at a concentration of 25 per cent. With increasing concentration, short episodes of fast activity appeared and finally the EEG developed 4 to 8 Hz waves. None of the previous studies described the electroencephalogram (EEG) which was related to cerebral circulation and metabolism. In the present study it was confirmed that cerebral metabolic stimulation with N_2O was accompanied by an increase in the CBF and EEG slowing, and possible factors which might affect $CMRo_2$, CBF and EEG during N_2O anesthesia were examined.

METHOD

Twenty three unpremedicated and 6 premedicated dogs with reserppine (weight 10.0 to 24.5 kg) were examined. Anesthesia was induced with halothane in 100 per cent oxygen. Then the dogs were intubated with the aid of intramuscular succinylcholine chloride (60 mg) and were ventilated artificially (Harvard pump NSH-34RH). Muscle relaxation was maintained by succinylcholine infusion (100 to 150 mg/hour) throughout the experiment. After intubation, halothane (1.0 to 1.5 per cent), in a gas mixture of 60 per cent nitrogen and 40 per cent oxygen, was administered to the dogs. Cannulae were placed in a femoral artery for blood sampling and pressure determination, and in a femoral vein for reinfusion of the blood through the pump. Another femoral vein was cannulated for drug administration and fluid infusion. The surgical preparations for direct measurement of the CBF were described in detail by Michenfelder et al[7]. In this technique, sagittal sinus blood is diverted to an external collecting system and returned by a pump to the femoral vein. The collecting blood is from the venous drainage of the anterior, superior and lateral portions of both cerebral hemispheres. After completion of the surgical preparation, the concentration of halothane in the inhaled gas mixture was adjusted to maintain an end-tidal concentration of 0.20 ± 0.01 (mean $\pm$ SE) per cent for the remainder of the study. The Pao_2 and $Paco_2$ were maintained at 175 ± 9 mmHg, 39 ± 2 mmHg, respectively, except in the dogs in which the effects of alteration of $Paco_2$ were tested. The oxygen content of arterial or sagittal sinus blood

was calculated from measurements of oxyhemoglobin (IL 182 Co-oximeter) and oxygen tension (IL 313 electrodes). The blood pH and $Paco_2$ were measured with appropriate electrodes (37°C). The EEG was recorded using parietal bipolar silver-silver chloride electrodes in all dogs, and was analyzed every 10 seconds with a frequency analyzer (NIHON KOHDEN MAF-5) throughout the study, except in the dogs pretreated with reserpine. The analyzed values were expressed as percentages of the integrated voltage of s(2 to 4 Hz), δ(4 to 8 Hz), α(8 to 13 Hz), β1(13 to 20 Hz) and β2 (20 to 30 Hz) waves. The endtidal halothane and N_2O concentrations were measured by gaschromatography (Shimazu, GC-4A) and the end-tidal CO_2 concentration was monitored by an infrared CO_2 analyzer (Toshiba-Beckman LB-1). The $CMRo_2$ was calculated as the product of the CBF and arterial-sagittal sinus blood content differences [$C(A\text{-}V)o_2$]. Cerebral circulatory index (CCI) and the cerebral vascular resistance (CVR) was calculated as the ratio of the CBF to $CMRo_2$ and as the ratio of the mean arterial pressure (MAP) to CBF, respectively. Control measurements were obtained over a 30 minute period, and mean value of $CMRo_2$ was calculated from five to eight consecutive determinations of the CBF and $C(A\text{-}V)o_2$.

Following the control measurements, in 7 dogs (Group I) the MAP, CBF and $C(A\text{-}V)o_2$ were then determined over a 120 minute period which was divided into two periods; an addition period and a withdrawal period. Each period lasted 60 minutes. At the beginning of the addition period the sudden substitution of N_2O for nitrogen was performed. Sixty minutes later, the sudden substitution of nitrogen for N_2O was performed. The measurement were made at 3, 5, 7, 10, 15, 30, 45 and 60 minutes after the start of each period.

In 4 dogs (Group II), thiamylal (8 mg/kg) was given intravenously over a 30 to 40 second period and 1 minute later the cerebral effects of 60 per cent N_2O were examined in the same manner as in Group I. The cerebrospinal fluid pressure (CSFP) was measured continuously through a needle (#19) inserted in the cisterna magna in Group I and II.

In 6 dogs (Group III) which were premedicated with reserpine (0.5 mg/kg daily for two-day period), on the third day the effects of 60 per cent N_2O were examined. In the immediate pre-study period the dogs were lethargic, anorexic, had diarrhea with tarry stool, and had irregular respiration, with decreased frequency and irregular and/or slow pulse.

In 6 dogs (Group IVa), the effects of hypocarbia, normocarbia, and hypercarbia on the CBF, $CMRo_2$ and EEG were examined without N_2O.

The respiratory rate and tidal volume were set to obtain a minimum $Paco_2$ (16 to 25 mmHg) and were kept constant throughout experiment. Various levels of $Paco_2$ were obtained by changing the concentration of inspired CO_2. The order of hypocarbia, normocarbia and hypercarbia was randomized. In 6 dogs (Group IVb), the effects of hypocarbia, normocarbia, and hypercarbia on the CBF, $CMRo_2$ and EEG were examined during N_2O.

In all dogs, the hemoglobin level was maintained at 12 ± 1 g/dl and the brain temperature was monitored by an epidural thermistor and maintained at 37.0 ± 0.2°C by external means. The results were tested for statistical significance by Student's t-test for paired data, and $P<0.05$ was considered to be significant.

RESULTS

The effects of 60 per cent N_2O (end-tidal) with a 0.2 per cent halothane background on cerebral circulation and metabolism are summarized in Table 1 (Group I). The end-tidal concentration of N_2O reached a peak within 10 minutes after the start of addition. The mean CBF and $CMRo_2$ increased significantly throughout the 60 minute period. The

Table 1. The effects of 60 per cent N_2O on the canine cerebral circulation, metabolism and cerebrospinal fluid pressure.

Time	MAP mmHg		CBF ml/100g/min		CVR mmHg/ml/100g/min		$CMRo_2$ ml/100g/min		CCI		$Psso_2$ mmHg		CSFP+ mmHg	
(min)	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Control	99	5	71	5	1.5	0.1	5.43	0.14	13.1	1.2	42	3	6	3
N_2O 5	102	8	143*	28	0.9*	0.2	6.14*	0.23	24.2	5.6	57*	6	17	6
10	97	8	143*	25	0.8*	0.2	6.37*	0.18	22.7*	4.2	56*	6	13	5
15	100	6	130*	18	0.9*	0.2	6.45*	0.20	20.5*	3.0	53*	5	12	4
30	95	7	111*	12	0.9*	0.2	6.58*	0.10	17.0*	2.0	49*	5	8	3
45	97	7	94*	9	1.1*	0.2	6.48*	0.12	14.6	1.5	47*	3	8	4
60	97	8	89*	8	1.1*	0.1	6.38*	0.17	14.1	1.4	44	3	7	4
N_2 5	101	9	70	4	1.5	0.1	5.70*	0.15	12.4	0.8	39	2	7	3
10	93	9	65	3	1.5	0.1	5.35	0.21	12.2	0.8	37	2	7	4
15	95	9	66	4	1.5	0.1	5.51	0.21	12.0	0.7	36*	2	7	4
30	93	8	65	4	1.4	0.1	5.55	0.20	11.7	0.7	37*	3	8	4
45	97	6	68	4	1.5	0.1	5.48	0.19	12.4	1.0	36*	2	9	4
60	97	5	66	4	1.5	0.1	5.44	0.15	12.4	1.0	34*	2	9	5

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

\+ 6 dogs

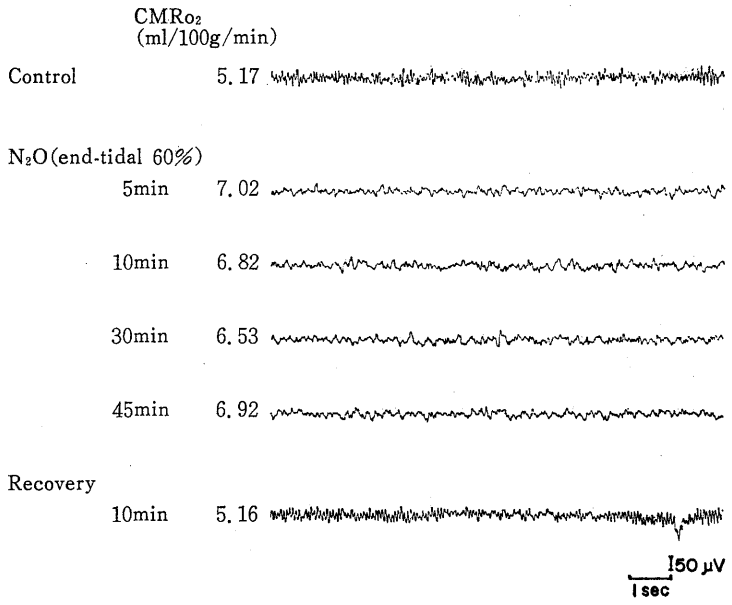

Fig. 1 A representative EEG with corresponding values of $CMRo_2$ during 60 per cent N_2O anesthesia.

mean CBF increased to a maximum of 203 per cent of the control at 7 minutes, and then it gradually declined to 125 and 130 per cent of the control at 45 to 60 minutes, resepectively. The $CMRo_2$ was steady at 120 per cent of the control value after 10 minutes. The mean CVR decreased significantly in a reverse relationship with the increase in the CBF, and the CSFP essentially paralleled the changes in the CBF. In the EEG, amplitude and frequency decreased and slow wave (δ, θ) activity became predominant. A representative EEG with corresponding values of the $CMRo_2$ is illustrated in Figure 1. These cerebral circulatory, metabolic and EEG changes returned to the control after nitrogen was substituted for N_2O.

The effects of N_2O after administration of thiamylal (8 mg/kg) are summarized in Table 2 (Group II). The mean CBF and $CMRo_2$ decreased parallelly to 78 per cent and 79 per cent, respectively, of the control value at 1 minute after the intravenous thiamylal. On the addition of N_2O, the $CMRo_2$ returned to the control and then increased significantly at 30 minutes after the start of N_2O, but the increase in the CBF was not significant. The changes in the CSFP paralleled those in the CBF. The EEG showed high voltage irregular slow wave activities for about 30 minutes after the injection of thiamylal, and then the EEG pattern

Table. 2 The effects of 60 per cent N_2O after the administration of thiamylal (8 mg/kg) on the canine cerebral circulation, metabolism, and cerebrospinal fluid pressure.

Time (min)		MAP mmHg		CBF ml/100g/min		CVR mmHg/ml/100g/min		$CMRo_2$ ml/100g/min		CCI		Pso_2 mmHg		CSFP+ mmHg	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Control		108	4	60	4	1.8	0.1	5.89	0.07	10.2	0.6	40	2	6	1
Thiamylal 8mg/kg		100	11	47*	5	2.2	0.3	4.70*	0.26	9.9	0.8	39	3	4	1
N_2O	3	101	13	49*	6	2.2	0.3	4.55*	0.19	10.6	1.1	42	3	4	1
	5	107	8	57	6	1.9	0.1	5.12*	0.18	11.0	0.8	44	3	5	1
	10	110	7	62	6	1.8	0.1	5.28*	0.13	11.7	1.1	45*	2	5	1
	15	108	6	60	6	1.9	0.1	5.32*	0.13	11.1	1.1	45*	2	5	1
	30	116*	6	64	6	1.9	0.1	5.80	0.22	10.9	0.8	42	3	6	1
	45	110	6	82	15	1.5	0.2	6.62*	0.31	12.1	1.5	45	4	7	1
	60	112	4	79	16	1.6	0.2	6.48*	0.24	12.0	2.0	46	4	6	1
N_2	5	106	6	56	5	2.0	0.2	5.95	0.19	9.4	0.6	39	4	5	1
	10	106	5	55*	5	2.0	0.2	5.86	0.14	9.3	0.6	39	4	5	1
	15	106	5	54*	6	2.0	0.2	5.72	0.17	9.5	0.8	40	3	5	1
	30	107	3	55	6	2.0	0.2	5.76	0.10	9.5	0.9	40	3	6	1
	45	109	4	56	6	2.0	0.2	5.65	0.14	9.9	0.8	40	3	6	1
	60	108	4	55*	5	2.0	0.2	5.80	0.17	9.4*	0.6	38	3	6	1

* Significantly different from control ($P<0.05$)
\+ 3 dogs

changed to that observed during N_2O inhalation alone. On the withdrawal of N_2O the EEG returned to the control pattern. A representative EEG with the corresponding value of $CMRo_2$ is illustrated in Figure 2. The per cent changes of the CBF and $CMRo_2$ (Group I, II) with the end-tidal concentration of N_2O and EEG frequency analysis are shown in Figures 3 and 4.

The effects of N_2O after the pretreatment with reserpine are summarized in Table 3 (Group III). The mean CBF and $CMRo_2$ increased significantly throughout the 60 minute period. The mean CBF increased to a maximum of 211 per cent of the control at 5 minutes, and then it gradually declined to 135 and 145 per cent of control at 30 to 60 minutes, respectively. The $CMRo_2$ reached a maximum of 127 per cent of the control at 7 minutes, and then fluctuated between 115 and 120 per cent of the control throughout the rest of the 60 minute period. The mean CVR decreased significantly in a reverse relationship with the increase in CBF. The mean CBF and $CMRo_2$ in Group III are compared with

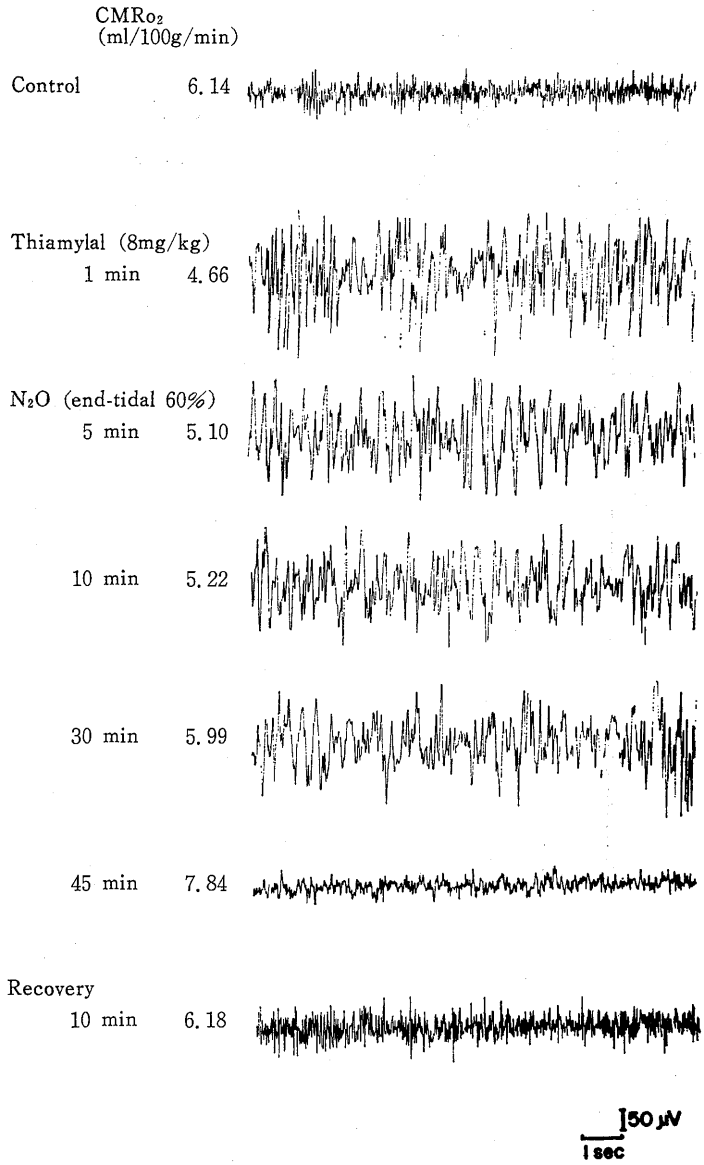

Fig. 2 A representative EEG with corresponding values of the $CMRo_2$ during N_2O anesthesia after the administration of thiamylal (8mg/kg).

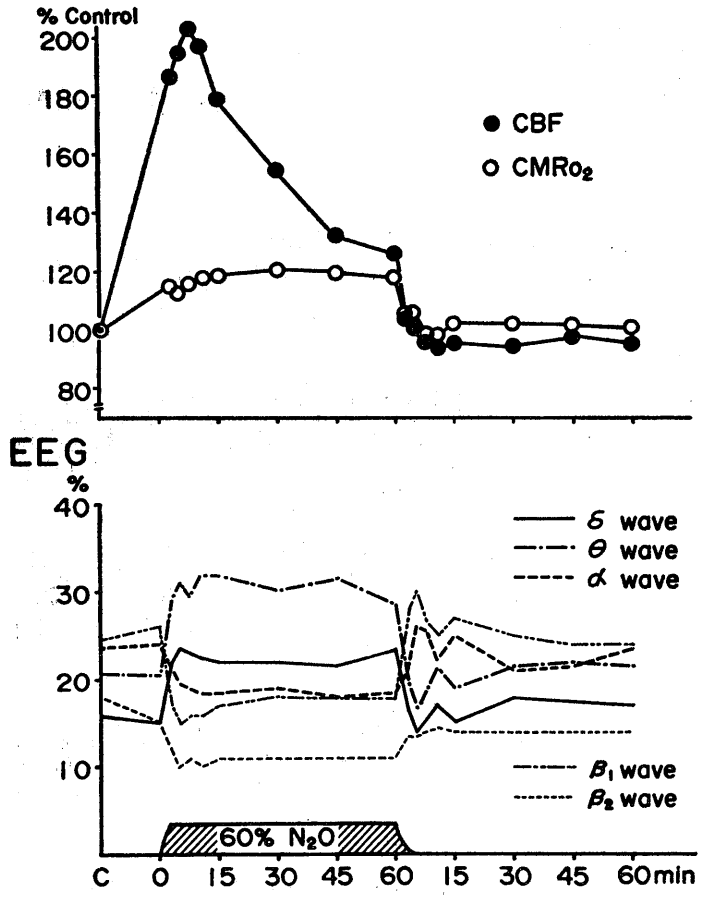

Fig. 3 The effects of N_2O on the CBF, $CMRo_2$ and EEG frequency analysis. θ wave activities are predominant.

those of Group I (Figure 5). The control EEG in Group III consisted of 6 to 10 Hz activity mixed with 16 to 22 Hz fast waves and was characterized by more predominant slow activity than that of Group I. With 60 per cent N_2O, the dominant frequency of the EEG dropped, until waves of 3 to 6 Hz were predominant, although there were slight variations with time and individual differences. On the withdrawal, the EEG returned to the control pattern (Figure 6).

The effects of hypocarbia, normocarbia, and hypercarbia on cerebral circulation and metabolism during control conditions and 60 per cent N_2O anesthesia are summarized in Table 4 (Group IVa: control, Group IVb: nitrous oxide). The relationships between the $CMRo_2$ and $Paco_2$

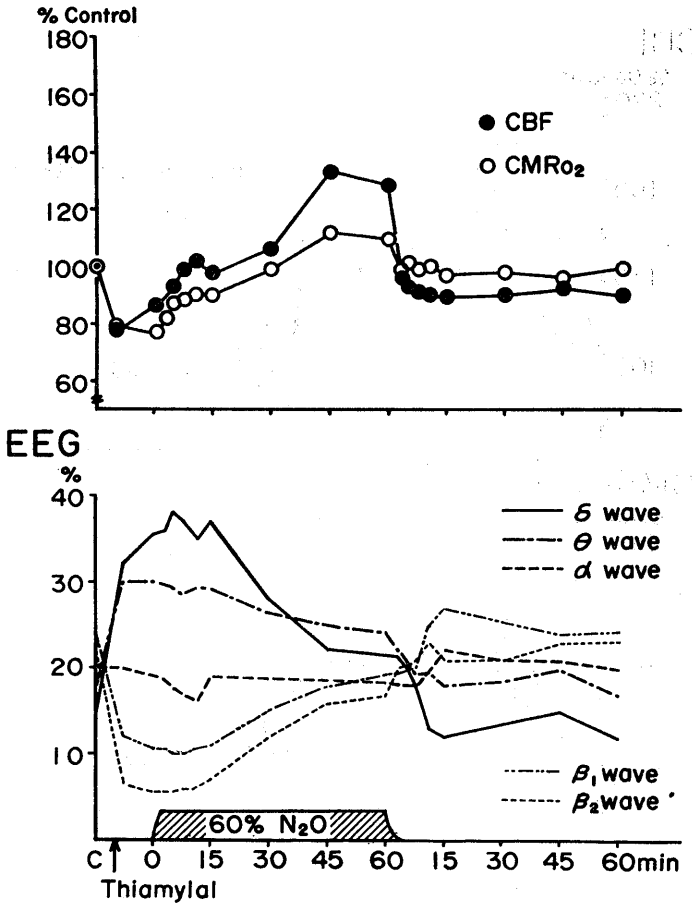

Fig. 4 The effects of N_2O anesthesia after the administration of thiamylal (8mg/kg) on the CBF, $CMRo_2$ and EEG frequency analysis. The arrow indicates the injection of thiamylal. δ wave activities are predominant.

Table. 3 The effects of 60 per cent N_2O on the cerebral circulation and metabolism in dogs pretreated with reserpine (total 1.0 mg/kg)

Time (min)	MAP mmHg		CBF ml/100g/min		CVR mmHg/ml/100g/min		$CMRo_2$ ml/100g/min		CCI		$Psso_2$ mmHg	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Control	81	3	60	4	1.4	0.1	5.49	0.30	11.1	0.7	33	2
N_2O 5	89*	2	128*	18	0.8*	0.1	6.88*	0.53	19.0*	3.0	49*	3
10	86	5	110*	16	0.9*	0.2	6.88*	0.48	16.7*	2.3	49*	5
15	82	4	106*	22	0.9*	0.2	6.50*	0.48	15.7	2.0	46*	4
30	87	5	89*	13	1.1*	0.2	6.24*	0.28	14.1	1.5	41*	3
45	85	3	87*	9	1.0*	0.1	6.68*	0.48	13.2	1.4	41*	2
60	82	4	80*	8	1.1*	0.1	6.23*	0.38	13.3	1.5	41*	3
N_2 5	86	4	68*	3	1.3	0.1	6.02*	0.22	11.4	0.8	36	2
10	84	4	65	2	1.3	0.1	5.87*	0.24	11.2	0.7	34	2
15	83	5	62	3	1.4	0.1	5.75	0.20	11.0	0.7	34	2
30	81	4	60	3	1.4	0.1	5.57	0.24	11.0	0.6	34	1
45	79	5	60	3	1.4	0.1	5.60	0.33	10.8	0.8	34	1

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

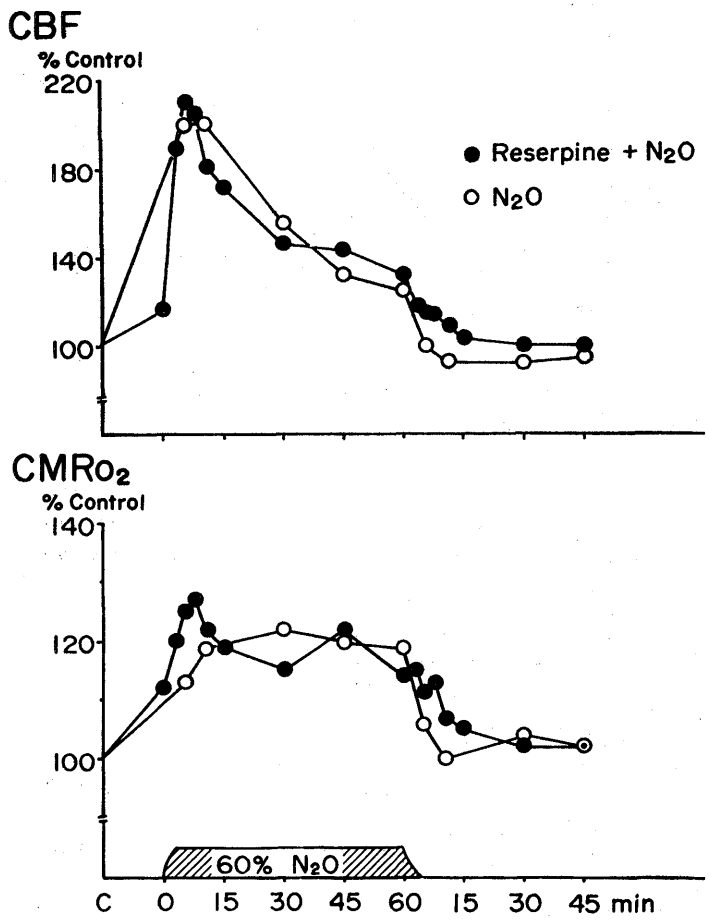

Fig. 5 The comparison of effects of N_2O on the CBF and $CMRo_2$ between the group pretreated with reserpine (Reserpine + N_2O) and the group not pretreated (N_2O).

without N_2O or with N_2O were tested and illustrated in Figure 8. There were no significant changes in the $CMRo_2$ between hypocarbia, normocarbia and hypercarbia with and without N_2O (Figure 7). The relationships between the CBF and $Paco_2$ without N_2O (1) or with N_2O (2) are expressed in the following equations:

$$CBF = 0.88\ Paco_2 + 30.3 \cdots\cdots (1)$$

$$CBF = 1.68\ Paco_2 + 22.4 \cdots\cdots (2)$$

Figure 8 shows individual values and regression lines. The regression coefficient, namely the reactivity of the cerebral vessels to the change in $Paco_2$, of the equation with N_2O is insignificantly larger than that

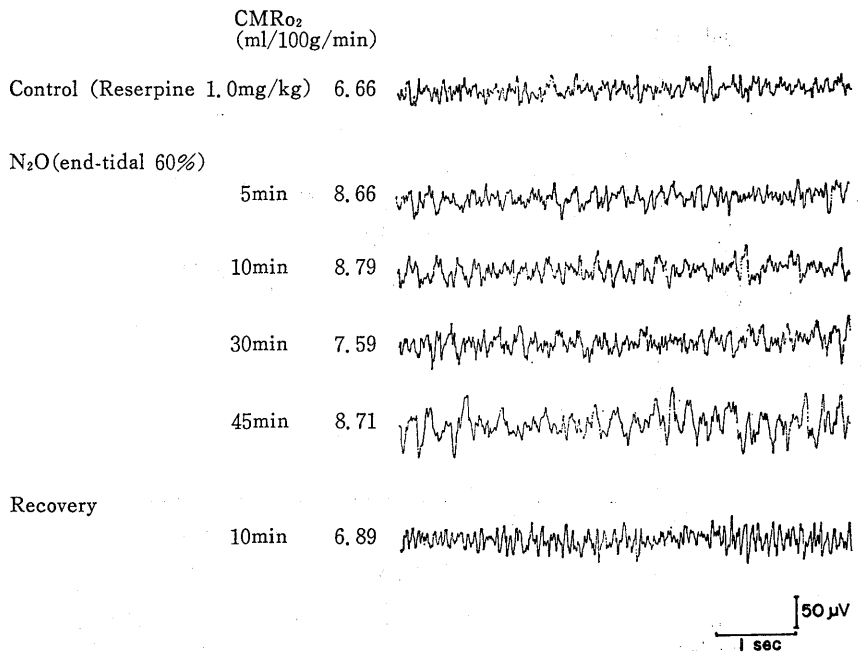

Fig. 6 A representative EEG with corresponding values of the $CMRo_2$ during N_2O anesthesia after the pretreatment with reserpine (total 1.0mg/kg).

Table. 4 The effects of hypocarbia, normocarbia, and hypercarbia on the canine cerebral circulation and metabolism during control conditions and during 60 per cent N_2O anesthesia.

Control

$PaCO_2$ mmHg		MAP mmHg		CBF ml/100g/min		CVR mmHg/ml/ 100g/min		$CMRo_2$ ml/100g/min		CCI		$Psso_2$ mmHg	
Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
22	1	109	7	50*	2	2.2*	0.2	5.41	0.31	9.4*	0.5	25*	1
40	1	112	7	62	2	1.8	0.1	5.45	0.22	11.4	0.4	36	2
58	2	111	6	85*	6	1.3*	0.1	5.17	0.30	16.4*	1.4	52*	2

Nitrous oxide (end-tidal 60%)

$PaCO_2$ mmHg		MAP mmHg		CBF ml/100g/min		CVR mmHg/ml/ 100g/min		$CMRo_2$ ml/100g/min		CCI		$Psso_2$ mmHg	
Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
22	1	114	7	63*	5	1.8*	0.1	6.27	0.38	10.5*	0.5	31*	1
41	2	116	5	82	6	1.4	0.1	6.33	0.24	13.1	1.0	42	3
64	1	112	7	134*	16	0.9*	0.1	6.22	0.32	21.8	3.1	65*	5

* Significantly different from normocarbia

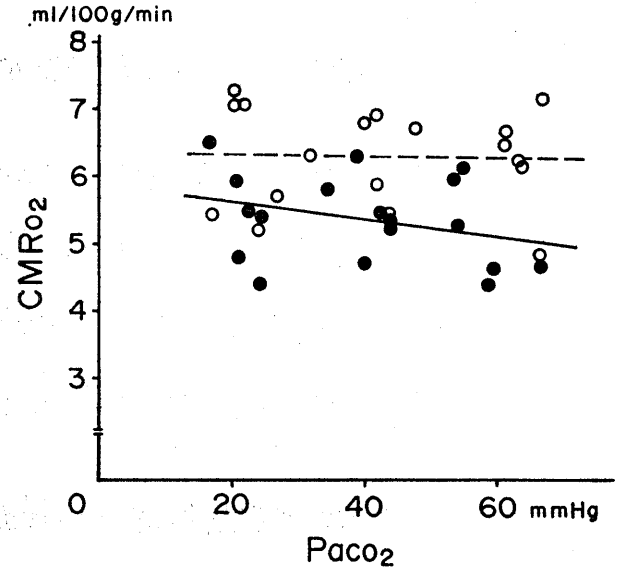

Fig. 7 The relationships between the $CMRo_2$ and $Paco_2$ without N_2O (solid line) and with N_2O (broken line). Solid circle indicates the individual value without N_2O and open circle with N_2O.

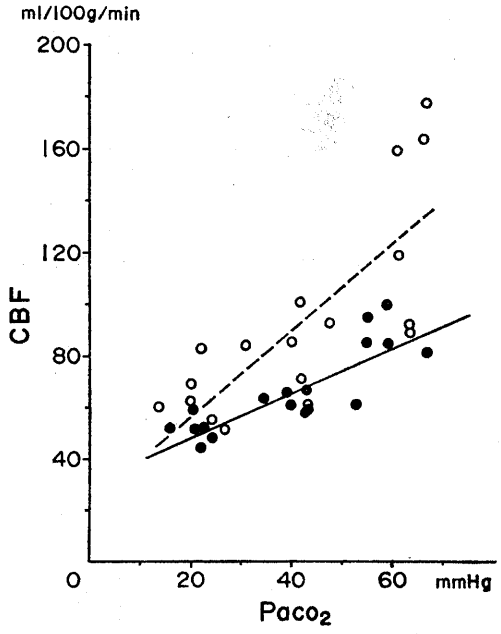

Fig. 8 The relationships between the CBF and $Paco_2$ without N_2O (solid line) and with N_2O (broken line) Solid circle indicates the individual value without N_2O and open circle with N_2O.

without N_2O. The mean CCI was significantly low in hypocarbia and high in hypercarbia as compared with normocarbia. The changes in EEG among the different levels of $Paco_2$ were variable and no consistent difference was found between Group IVa and IVb, although in some cases the EEG tended to slow with either a high or low $Paco_2$.

DISCUSSION

The present study demonstrated that 60 per cent N_2O is a cerebral metabolic stimulant, as evidenced by the significant increase in the $CMRo_2$, which reached a peak within 10 minutes, during 0.2 per cent halothane anesthesia in unpremedicated dogs. The time course of the changes in the $CMRo_2$ paralleled the change in the end-tidal concentration of N_2O and the maximum increase was 21 per cent. The cerebral metabolic stimulatory effects of N_2O (70 per cent) were reported previously by Theye and Michenfelder[6] in dogs. In their study, the magnitude of increase in the $CMRo_2$ was 11 per cent in the absence of halothane or with 0.1 per cent halothane as background anesthesia. The quantitative difference between their study and ours might be due to the fact that dogs received total spinal anesthesia, vagotomies and cervical sympathectomies in their study. It had been reported that spinal anesthesia produces a small (14 per cent) but significant decrease in the $CMRo_2$[8]. Therefore, a 21 per cent increase in the $CMRo_2$ observed in our study is well compatible with the study by Theye and Michenfelder[6].

Wollman et al.[5] reported the effects of 70 per cent N_2O in man immobilized with d-tubocurarine. They observed 23 per cent decrease in the $CMRo_2$ with a decrease in body temperature which affected the results. The differences in methodology might explain the discrepancies between the studies. In man, the CBF was measured by a modified Kety-Schmidt method, and hence its value represents the mean blood flow for the whole brain. However, the present study and Theye's study[6] measured the cerebral hemispheric blood flow, especially the cortical blood flow. Such difference have also occured with ketamine. Takeshita et al.[9] reported a striking increase in the CBF (whole brain) without significant change in the $CMRo_2$ during ketamine anesthesia in man, whereas Dawson et al.[10] found a similar increase in the CBF (hemispheric blood flow) was accompanied by a significant increase in the $CMRo_2$ in dogs.

Previous studies on N_2O indicated either no change[11-13] or depression[14] of cerebral respiration in vitro. The depressive effect of N_2O was further supported by Nahrwold and Cohen[15], who reported the decrease

of mitochondrial respiration in the rat liver. However, the present study clearly indicates cerebral stimulatory effect of N_2O and suggests the difficulty of transfering in vitro data to in vivo situations.

It has been reported that halothane[16] decreases the $CMRo_2$ with accompanying EEG slowing. However, ether[16] does not cause a significant change in the $CMRo_2$, though progressive EEG slowing becomes apparent as anesthesia deepens. Among the inhalation agents, N_2O is a unique drug which causes an increase in the $CMRo_2$ with an increased CBF and EEG slowing. It has been generally believed that EEG slowing is a reflection of decreased cerebral function[2]. However if one accepts the idea that the observed change in the $CMRo_2$ is a net change of neuronal activity, then the EEG slowing obsesved during N_2O must be interpreted as neuronal excitation. Therefore, an anesthetic state can be an excitatory state at least at cortical level. With prior administration of thiamylal, an increase in the CBF above control value was not observed until 30 to 45 minutes after the start of inhalation of N_2O. The mean $CMRo_2$ significantly decreased for the first 15 minute during N_2O. After 45 minutes the CBF increased to 130 per cent of the control, which was about same as the change observed during N_2O inhalation at 0.2 per cent halothane background anesthesia, while the $CMRo_2$ was 110 per cent of control value. This indicates that thiamylal blocks the circulatory and metabolic stimulating effect of N_2O. Similar findings have also been reported with ketamine by Dowson et al.[10]. Thiamylal produced a typical EEG change (high voltage irregular slow waves) and a decreased $CMRo_2$. However, the typical EEG with thiamylal disappeared as the effect of thiamylal wore off and finally was replaced by slow wave activity which is observed with N_2O alone. Thus, EEG slowing during anesthesia was accompanied by either depressed, stimulated or unchanged cerebral metabolism. In the present study it is demonstrated that the generalization that the anesthetic state is accompanied by a reduction in the $CMRo_2$ and CBF with a concomitant slowing of EEG, suggested by Ingvar[17] is not applicable to all anesthetic states.

There is another aspect of cerebral metabolic stimulation with N_2O. Michenfelder and Theye[8] reported the modifying effects of catecholamine on the $CMRo_2$ during cyclopropane anesthesia and found that cyclopropane decreased the $CMRo_2$ in reserpinized dogs. Similarly, in this study there may be cerebral metabolic stimulating effects through activation of the sympathoadrenal system.[18] To examine this possibility, one group of dogs were pretreated with reserpine. Reserpine is known to release and thereby lessen stores of epinephrine and norepinephrine throughout the body. In pretreated dogs the effect of N_2O on the $CMRo_2$ was similar

to that of untreated dogs. The responese of the CBF to N_2O was not convincingly modified by pretreatment with reserpine, either. It is possible that the dogs were not fully reserpinized. However, the potential magnitude of this effect is exemplified by a reported 98 per cent depletion in norepinephrine levels of the dog heart after two daily doses of 0.5 mg/kg[19]. Holzbauer and Vogt[20] reported that the norepinephrine concentration of the cat's hypothalamus is reduced by one injection of reserpine (0.4 mg/kg) from its normal value of 1.4 μg/g to between 0.20 μg/g and 0.86 μg/g fresh tissue. Miller et al.[21] described a decrease of 23 per cent in the minimum alveolar anesthetic concentration (MAC) with reserpine (0.8 mg/kg) in rats. Therefore, the present dose of reserpine (1.0 mg/kg) was considered to be sufficient to modify the sympathetic stimulation of N_2O and MAC. The present study suggests that sympathoadrenal overactivity with N_2O does not contribute to an increase in the CBF and $CMRo_2$.

It has become apparent that N_2O increases the CBF remarkably, with a concomitant decrease in the CVR. A rapid initial rise in the CBF occured within 5 minutes, and then the CBF gradually decreased over the 60 minute period, although it remained greater than the control CBF. Using the same preparation, Theye and Michenfelder[6] reported a greater CBF with 70 per cent N_2O than with 70 per cent nitrogen, which was due to a lower CVR rather than to a higher perfusion pressure, and was associated with a greater $CMRo_2$. The mechanism of this time course change in the CBF can not be explained from the present data, but it deserves some discussion. The initial increase in the CBF might be explained by the direct effect of N_2O on cerebral vascular smooth muscles, since the CBF reached a peak, when the endtidal concentration of N_2O also reached a peak. If the direct effect of N_2O on cerebral vasculature is the only factor, the CBF should be stable once the N_2O concentration reaches a plateau. Therefore, some other factors must be involved in the time course of the CBF during N_2O. McDowall and Harper[22] reported that adding halothane to the nitrous oxide-oxygen anesthetic mixture caused a progressive decrease in the CBF, with increasing duration of administration, to a level approximately proportional to the observed reduction in metabolic rate. Therefore, the metabolic component can not be excluded in the time course of the CBF. The cerebral oxygenation during N_2O seems to be well maintained by the disproportionate increase in the CBF to the $CMRo_2$ as evidenced by the elevated CCI and sagittal sinus venous oxygen tension ($Psso_2$). Sakabe[24] found that the alteration in the $Paco_2$ affects $CMRo_2$ and EEG during enflurane anesthesia. However, in this study no significant effect of

$Paco_2$ on $CMRo_2$ during N_2O was observed.

The relationships between the $Paco_2$ and CBF, in a range of $Paco_2$ in Group IVa and IVb were linear as expected. Thus the CO_2 response with N_2O was well preserved. Fujishima et al.[23] reported that the capacity of cerebral vessels to dilate or constrict in response to changes in the $Paco_2$ was influenced by cerebral oxygen consumption. However, in the present study there was only an insignificant change in the regression lines between both groups despite the apparent change in the $CMRo_2$. A rapid elevation in the CSFP with N_2O is considered to be due to the rapid increase in the CBF. The remarkable increase observed in the CSFP is also possible in man, as reported by Henriksen and Jorgensen[25]. It is believed that N_2O has only mild effects on the brain and N_2O supplemented with a neuroleptnarcotic combination and a muscle relaxant is the proper choice for neurosurgical patient, because narcotics [26-29] and the neurolept-narcotic combination[30-34] decreases or does not change the CBF, $CMRo_2$ and CSFP. However, if the results of the present study are applicable to humans, such a concept is not necessarily acceptable. For the safe use of about 60 per cent N_2O, in the neurosurgical patients with decreased intracranial compliance, prior administration of thiopental and perhaps hyperventilation are highly recommended.[35,36]

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