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

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Abstract. The effects of sciatic nerve stimulation on the electroencephalogram (EEG), cerebral metabolic rate for oxygen ($CMRo_2$) and cerebral blood flow (CBF) were investigated at five different levels of thiopental anesthesia. Thiopental was infused intravenously at the constant rate of 23 mg/kg/hour for 2 hours, and anesthetic levels at 10 (plasma concentration of thiopental 15 ± 2 μg/ml), 30 (27 ± 3), 60(37 ± 6), 90(42 ± 6) and 120 minutes (49 ± 6) after the start of infusion were designated levels I, II, III, IV and V, respectively. With increasing dose of thiopental, the EEG changed from fast wave activity to irregular slow wave activity and then burst suppression. These EEG changes were accompanied by the progressive reduction of $CMRo_2$ and CBF, decreasing to 58 and 59 per cent of the value before thiopental at level V, respectively. The effects of stimulation for 5 minutes were tested at each level. At level I the mean $CMRo_2$ and CBF increased to 110 and 107 per cent of control, respectively, accompanied by EEG activation. At level II the $CMRo_2$ and CBF increased at 1 minute to 106 and 107 per cent of control, respectively, accompanied by the EEG activation. At the three deepest levels the EEG, $CMRo_2$ and CBF remained unchanged. These results suggest that tight coupling between the EEG, $CMRo_2$ and CBF exists during thiopental anesthesia.

Key Words: EEG, brain; metabolism, blood flow, thiopental

Introduction

A sufficient dose of barbiturate to produce an anesthetic state is known to cause electroencephalographic (EEG) slowing which is accompanied by the reduction of the cerebral metabolic rate for oxygen ($CMRo_2$) and cerebral blood flow (CBF)[1]. This suggests that during barbiturate anesthesia a close relationship between function, metabolism and blood flow exists, as observed during wakefulness[2] and in chronic brain disease[3]. However, such a relationship does not necessarily exist in all anesthetic circumstances, since it had been known that volatile anesthetics cause EEG slowing and a decrease in $CMRo_2$, but an increase in CBF[4]. These studies of $CMRo_2$ and CBF have been concerned only with the effect of anesthetics without stimulation and this approach may not allow us to examine the ralationship between function, metabolism and blood flow

during anesthesia. In this author's laboratory, Kuramoto and his associates[5] studied modification of EEG, $CMRo_2$ and CBF responses to stimulation by halothane, methoxyflurane, nitrous oxide and morphine, and suggested that the coupling of $CMRo_2$ and CBF would vary with anesthetics and anesthetic levels. Accordingly, in this study EEG, $CMRo_2$ and CBF responses to stimulation were examined during thiopental anesthesia in the dog.

Materials and Methods

Ten unpremedicated mongrel dogs weighing 10 to 21 kg were anesthetized with halothane, 1 to 1.5 per cent inspired, in oxygen and nitrogen. Succinylcholine was given to facilitate tracheal intubation and was administered at 1 mg/kg/hour to maintain muscle paralysis. Ventilation was controlled with a Harvard pump during the measurement to maintain $Paco_2$ at 38 ± 0.5 (SE) torr. Pao_2 was maintained at 187 ± 2 torr by adjustment of ventilation and inspired oxygen concentration. Esophageal temperature and hemoglobin levels were maintained at 37 ± 0.1°C and 12 ± 0.2 g/dl, respectively. Mean arterial pressure (MAP) during the control measurement was maintained above 70 torr in all dogs. In order to maintain this pressure level, phenylephrine, which is reported to have no effect on cerebral metabolism and circulation[6], was administered, only when MAP decreased below 70 torr with deepening of anesthesia despite appropri-ate blood replacement. Both femoral arteries were cannulated for blood sampling and pressure measurement, 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. Their proximal ends were then gently placed on bipolar silver-silver chloride electrodes separated by 1 cm. Sciatic nerve temperature was maintained by circulating warmed liquid paraffin around the exposed area. EEG activation was accomplished by application of supramaximal rectangular stimuli (6 volts, 0.1 msec, 100 Hz) for 5 min.

The surgical preparation used for the measurement of hemispheric CBF was originally described by Michenfelder et al[7]. Lidocaine, 5 mg/kg, 0.5 per cent solution was injected into the skin and muscle of the head and at the area where the cannulas were placed. Additional lidocaine (half of the initial dose) was given hourly. After the animal was heparinized by an initial dose of 3 mg /kg (0.5 mg/kg/hour, subsequently), cannulation of the sagittal sinus was performed. The drained blood was returned to the left external jugular vein through the draining cannula. An electromagnetic flowmeter probe (lumen diameter 3 mm) was incorporated 1 cm away from the draining portion of the sinus. To ensure exact measurements, the electromagnetic flowmeter (Nihon Kohden MF-46) incorporated a nonocculusive zero and a 3 second time constant. In addition, the electromagnetic flowmeter was frequently calibrated by direct timed measurements of the sagittal sinus blood flow. The percentage of the total brain weight drained from the sagittal sinus was determined by injecting vinyl acetate at the completion of each experiment. This figure was used to convert units of flow from ml/min to ml/100g/min. Oxygen content of the arterial and sagittal sinus blood was calculated from measurement of oxyhemoglobin (IL 282 CO-oxymeter) and oxygen tension (ABL-2 electrode). pH and Pco_2 values were measured with appropriate electrodes. The $CMRo_2$ was calculated as the product of CBF and the difference in oxygen contents of the arterial and sagittal sinus blood. Cerebral vascular resistance (CVR) was calculated as the ratio of MAP to CBF. The EEG was continuously recorded using parietal bilateral silver-silver chloride electrodes.

After completion of the surgical preparations, the inspired halothane concentration was decreased to 0.3 per cent and at least one hour was allowed to elapse before the start of the experiment. The mean value of $CMRo_2$ and CBF was calculated from 5 to 7 consecutive determinations of $CMRo_2$ and CBF before the start of thiopental infusion. After the value before thiopental had been obtained, thiopental was infused intravenously at the constant rate of 23 mg/kg/hour for 2 hours. The effects of sciatic nerve stimulation on $CMRo_2$ and CBF were examined at 10, 30, 60, 90 and 120 minutes after the start of infusion. The anesthetic levels at 10, 30, 60, 90 and 120 minutes were designated level Ⅰ, Ⅱ, Ⅲ, Ⅳ and Ⅴ, respectively. At each levels of anesthesia, a control measurement was obtained over the first 5 minutes by measuring $CMRo_2$ and CBF at 1-minute intervals, and the mean value was calculated from these 5 determinations. Following this control measurement, stimula-

tion to both sciatic nerves was supplied. During the stimulation, CBF and MAP were measured and samples of arterial and sagittal sinus blood for $CMRo_2$ determination were drawn at 1-minute intervals. A decrease in amplitude or increase in frequency, or both, were considered a manifestation of EEG activation. Plasma thiopental concentrations were measured at each level by gas chromatography (Shimadzu GC-4). All data were subjected to analysis of variance. $P<0.05$ was considered significant.

Results

The mean $CMRo_2$ and CBF before thiopental were 5.99 ± 0.17 ml/100g/min and 58.5 ± 3.1 ml/100g/min, respectively. The EEG before thiopental mainly consisted of 13-20 Hz wave. At level I to III EEG consisted of 2 to 8 Hz superimposed by 8 to 13 Hz wave and then the amplitude tended to

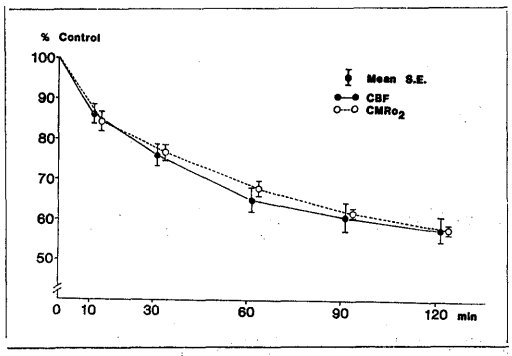

Fig. 1 Changes in mean $CMRo_2$ and CBF with increasing dose of thiopental (23 mg/kg/hour infusion).

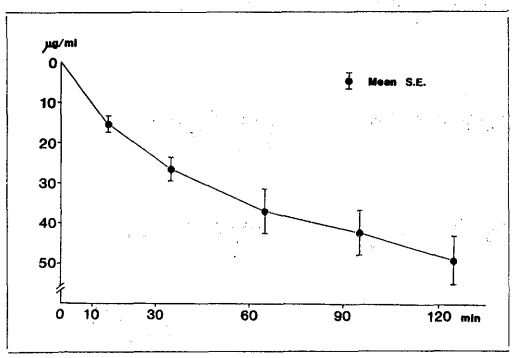

Fig. 2 Changes in plasma thiopental concentration with increasing dose (23 mg/kg/hour infusion).

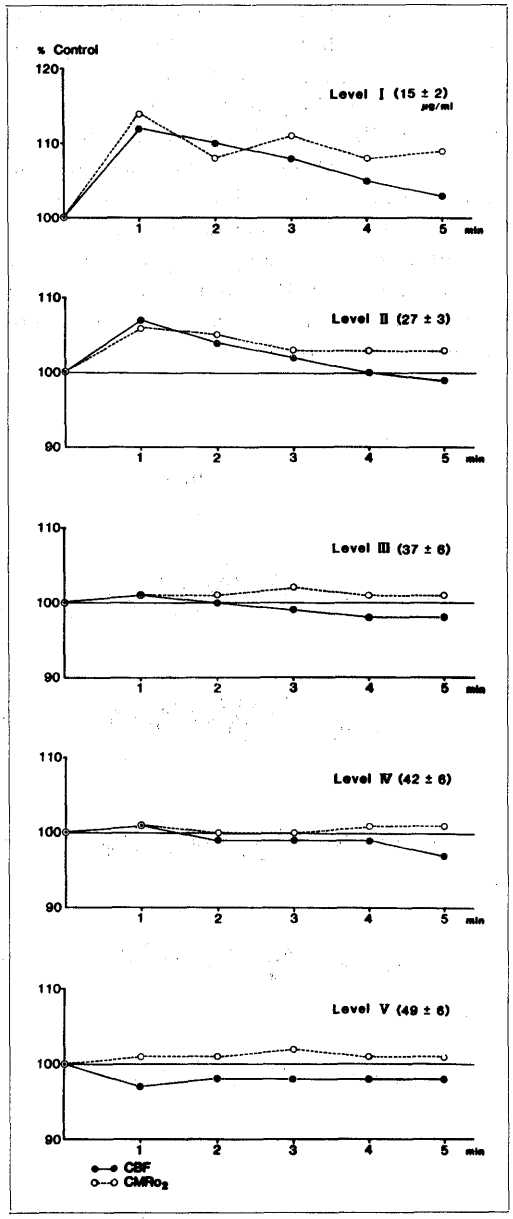

Fig. 3 Time course of $CMRo_2$ and CBF expressed as per cent of control at five different levels.

decrease (level Ⅳ). At level Ⅴ burst suppression was recorded in all dogs. The per cent control of $CMRo_2$ and CBF during thiopental infusion of 23 mg/kg/hour is illustrated in Fig. 1. Plasma thiopental concentrations were shown in Fig. 2, and were 15±2, 27±3, 37±6, 42±6 and 49±6 μg/ml at level Ⅰ, Ⅱ, Ⅲ, Ⅳ and Ⅴ, respectively. At 10 minutes of thiopental infusion (level I), the mean $CMRo_2$ and CBF decreased to 84 and 86 per cent of the value before thiopental, respectively. Thereafter, the mean $CMRo_2$ and CBF decreased progressively. At 120 minutes of thiopental infusion (level V) the mean $CMRo_2$ and CBF decreased to 58 and 59 per cent of the value before thiopental, respectively.

The effect of sciatic nerve stimulation on cerebral metabolism and circulation during thiopental anesthesia is summarized in the Table Ⅰ, Ⅱ, Ⅲ, Ⅳ and Ⅴ. The time course of the per cent control of $CMRo_2$ and CBF is shown in Fig. 3. Representative EEG patterns are shown in Fig. 4. At level I the mean $CMRo_2$ and CBF increased to 110 and 107 per cent of control during the stimulation, respectively. With stimulation the EEG was highly activated, thereafter displaying little tendency to return to the control pattern. At level Ⅱ the $CMRo_2$ and CBF increased significantly at the first two and first minute, respectively, and then returned to the control level. The EEG initially showed an activated pattern but

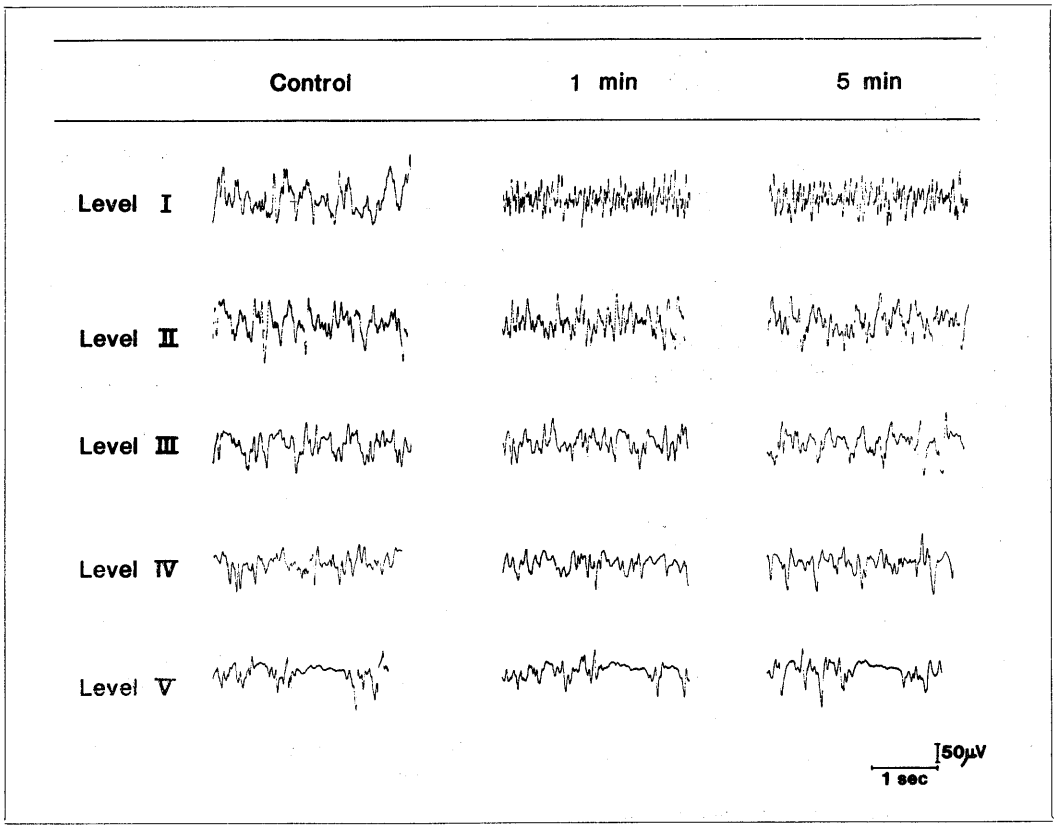

Fig. 4 Representative EEG patterns, 1 and 5 min, respectively after the start of stimulation at five different levels.

Table I Effects of sciatic nerve stimulation on cerebral circulation and metabolism during thiopental anesthesia (Level I)

Time after stimulation (min)	MAP (torr)	CBF (ml/100g/min)	CVR (torr/ml/100g/min)	$CMRo_2$ (ml/100g/ min)
Control	94±5	50.3 ±2.7	1.93 ±0.15	5.04 ±0.20
1	96±7	56.3*±3.0	1.74*±0.15	5.76*±0.23
2	94±5	55.1*±2.9	1.77*±0.14	5.46*±0.17
3	92±4	54.2*±3.0	1.76*±0.14	5.57*±0.20
4	91±4	52.6*±2.9	1.79*±0.15	5.42*±0.19
5	91±5	51.9 ±3.1	1.82 ±0.15	5.50*±0.21

Mean±SE
* Significantly different from control ($P<0.05$)

Table II Effects of sciatic nerve stimulation on cerebral circulation and metabolism during thiopental anesthesia (Level II)

Time after stimulation (min)	MAP (torr)	CBF (ml/100g/min)	CVR (torr/ml/100g/min)	$CMRo_2$ (ml/100g/min)
Control	91 ±4	44.4 ±2.8	2.12 ±0.14	4.59 ±0.18
1	85*±5	47.6*±3.3	1.87*±0.16	4.85*±0.22
2	87 ±4	46.3 ±3.3	1.96*±0.15	4.84*±0.24
3	86*±4	45.4 ±3.3	1.98*±0.16	4.72 ±0.23
4	85*±4	44.4 ±3.2	2.00*±0.16	4.71 ±0.24
5	85*±4	44.1 ±3.3	2.01 ±0.16	4.73 ±0.24

Mean±SE
* Significantly different from control ($P<0.05$)

Table III Effects of sciatic nerve stimulation on cerebral circulation and metabolism during thiopental anesthesia (Level III)

Time after stimulation (min)	MAP (torr)	CBF (ml/100g/min)	CVR (torr/ml/100g/min)	$CMRo_2$ (ml/100g/min)
Control	88 ±4	38.2±2.9	2.42 ±0.21	4.09±0.19
1	74*±5	38.5±2.9	2.04*±0.22	4.13±0.20
2	79*±5	38.0±3.0	2.19*±0.23	4.13±0.21
3	78*±5	37.8±3.0	2.18*±0.23	4.17±0.21
4	77*±6	37.5±3.0	2.17*±0.22	4.13±0.20
5	77*±5	37.4±2.9	2.18*±0.23	4.12±0.17

Mean±SE
* Significantly different from control ($P<0.05$)

Table Ⅳ Effects of sciatic nerve stimulation on cerebral circulation and metabolism during thiopental anesthesia (Level Ⅳ)

Time after stimulation (min)	MAP (torr)	CBF (ml/100g/min)	CVR (torr/ml/100g/min)	$CMRo_2$ (ml/100g/min)
Control	88 ±4	36.1±3.2	2.60 ±0.24	3.71±0.14
1	73*±4	36.3±3.4	2.21*±0.24	3.76±0.15
2	77*±4	35.7±3.4	2.33*±0.23	3.72±0.16
3	78*±4	35.7±3.3	2.33*±0.23	3.72±0.15
4	77*±4	35.7±3.3	2.32*±0.23	3.73±0.14
5	76*±4	35.2±3.3	2.32*±0.22	3.74±0.14

Mean±SE
* Significantly different from control ($P<0.05$)

Table Ⅴ Effects of sciatic nerve stimulation on cerebral circulation and metabolism during thiopental anesthesia (Level Ⅴ)

Time after stimulation (min)	MAP (torr)	CBF (ml/100g/min)	CVR (torr/ml/100g/min)	$CMRo_2$ (ml/100g/min)
Control	84 ±4	34.4±3.1	2.63 ±0.25	3.46±0.12
1	76*±4	33.5±3.0	2.41*±0.24	3.48±0.13
2	77*±4	33.7±3.1	2.44*±0.25	3.49±0.12
3	76*±4	33.8±3.1	2.42*±0.25	3.52±0.12
4	77*±5	33.8±3.0	2.45*±0.26	3.50±0.12
5	78*±5	33.7±3.0	2.46 ±0.25	3.50±0.12

Mean±SE
* Significantly different from control ($P<0.05$)

tended toward the control pattern at the end of stimulation. At levels Ⅲ, Ⅳ and Ⅴ the EEG, $CMRo_2$ and CBF were unaffected by the stimulation.

Discussion

The present study clearly indicates a dose-dependent reduction of $CMRo_2$ (as a reflection of metabolism) and CBF with increasing dose of thiopental. The EEG (as a reflection of function) slowing was accompanied by a parallel reduction of $CMRo_2$ and CBF, suggesting that CBF met the oxygen demand of the cerebral hemispheres. Stullken et al[8] reported that with infusion of thiopental at 23 mg/kg/hour for 2 hours, $CMRo_2$ decreased to about 60 per cent of control. The magnitude of decrease in $CMRo_2$ in the present study is in good agreement with their work. Although it is difficult to compare the anesthetic potency of thiopental with inhalational anesthetics, the magnitude of decrease in $CMRo_2$ produced by thiopental is marked when compared with inhalational anesthetics. At 1 minimum alveolar concentration (MAC) of halothane, methoxyflurane and enflurane, the decrease in $CMRo_2$ is 13, 22 and 17 per cent, respectively[4]. It has been reported that the anesthetic level at plasma thiopental concentration of 39 to 42 μg/ml is equivalent to that

produced by 1 MAC of inhalational agents in man[9]. There is no reason to assume that a plasma thiopental level equivalent to 1 MAC of inhalational anesthetics in man is largely different from that in the dog since MACs are close to those in man. In this study $CMRo_2$ decreased 38 and 42 per cent of the value before thiopental at plasma thiopental concentrations of 42 ± 6 and 49 ± 6 μg/ml, respectively. Thus, thiopental is potent cerebral metabolic depressant and if this result is applicable to man, it can be said that barbiturate at a dose sufficient to produce burst suppression produces a marked decrease in $CMRo_2$ which is not easily obtained with inhalational anesthetics.

The present study indicates the presence of coupling between the EEG and $CMRo_2$ during thiopental anesthesia. The EEG activation by sciatic nerve stimulation was consistently accompanied by an increase in $CMRo_2$ during thiopental anesthesia. Furthermore, the individual time course of the changes in $CMRo_2$ was closely related to that of the EEG patterns, and there was a coupling between EEG, $CMRo_2$ and CBF at all anesthtetic levels. The author had anticipated an EEG activation even during deep thiopental anesthesia (level Ⅳ and Ⅴ), since barbiturates are known to be less potent in blocking noxious stimuli[10]. However, cerebral metabolic and circulatory responses to electrical stimulation of the peripheral nerve rapidly became minimal with increasing dose of thiopental.

Meyer et al[11] reported no significant change in the EEG, $CMRo_2$ and CBF during stimulation of the femoral nerve in two anesthetized monkeys. Unfortunately, the inexact nature of their reported anesthetic conditions and the differences in methodology make detailed comparison difficult. Langfitt and Kassell[12] reported that stimulation of the brainstem 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. They concluded that the most likely explanation for the cerebral vasodilation was a neurogenic mechanism because of the very short time between stimulation and response. However, they did not measure $CMRo_2$, making examination of the relationship between $CMRo_2$ and CBF impossible. Recent studies have emphasized that regional changes in CBF are related to the functional state of the awake brain[3,13]. In rabbits anesthetized with chloralose and urethane, Anderson et al[14] reported that increased CBF due to sciatic nerve stimulation paralleled an increase in local metabolism, and that the increase in CBF was independent of the change in MAP, since sciatic nerve stimulation resulted in a decrease in MAP. The parallel change in $CMRo_2$ and CBF in the present study suggests that cerebral vasodilatation occurs in response to demand for oxygen during increased neuronal activities. Kuramoto and his associates[5] studied modification of the relationship between the EEG, cerebral metabolism and blood flow by sciaticn nerve stimulation during various anesthesia. During halothane anesthesia, sciatic nerve stimulation produced a striking increase in CBF even at the stage where no EEG and $CMRo_2$ responses were seen. In contrast, with morphine, which is a mild cerebral vasoconstrictor, there was a coupling between $CMRo_2$ and CBF during stimulation. They suggested that coupling between $CMRo_2$ and CBF may be related to the cerebral vascular effects of individual anesthetics, and appears to be dependent on whether a specific drug dilates or constricts cerebral vessels. The present study supports their suggestion, since thiopental is known to be a potent cerebral vasoconstrictor.

In the present study, the mean MAP decreased with stimulation at levels Ⅱ, Ⅲ, Ⅳ and Ⅴ. Such a decrease in MAP was also observed during sciatic nerve stimulation

under deep halothane or methoxyflurane anesthesia[5]. However, during light halothane, methoxyflurane and morphine anesthesia, MAP increased with peripheral stimulation [5]. This suggests that individual effects of anesthetics on vasomotor response to peripheral stimulation may be variable.

It is well known that in neurosurgical anesthesia, an increase in CBF may be harmful, especially for the patient who already has an increased intracranial pressure[15]. In this respect, thiopental does not cause a striking increase in CBF with peripheral stimulation as seen in halothane, and hence seems to be a suitable agent for the patient with increased intracranial pressure. In summary, during thiopental anesthesia there was tight coupling between the EEG, $CMRo_2$ and CBF. At the EEG stage of burst suppression, there was no cerebral metabolic and circulatory responses to peripheral stimulation in the dog.

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