Circulatory and Metabolic Changes in the Brain during Induced Hypotension

— comparison among trimetaphan, glycerin trinitrate and prostaglandin E_1 —

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Induced hypotension was carried out using trimetaphan (TMP), glycerin trinitrate (GTN) and prostaglandin E_1 (PGE$_1$) in 45 patients received elective abdominal surgery under anesthesia with enflurane in N_2O/O_2 in order to evaluate and compare the effects of these three agents on cerebral circulation and metabolism. Upon reduction of mean arterial blood pressure to 60–65 mmHg, cerebral blood flow decreased in the TMP and GTN groups but increased in the PGE$_1$ group. The changes were quite proportional to those in cardiac index in the three groups. Cerebral oxygen consumption decreased only in the TMP group. Changes in cerebrospinal fluid pressure were not in parallel with those in cerebral blood flow. The former decreased slightly in the TMP group but increased in the GTN and PGE$_1$ groups. These results offered a great caution for induction of artificial hypotension using these agents. (Key words: induced hypotention, cerebral blood flow, trimethaphan, glycerin trinitrate, prostaglandin E_1)

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Major problems related to induced hypotension during anesthesia include tissue hypoxia due to reduction in the blood flow to organs[1-3]. In particular, the information on the effects of induced hypotension on cerebral perfusion has been lacking because of extreme difficulty to determine it clinically. In the present study, we conducted induced hypotension using three most commonly used agents, trimetaphan (TMP), glycerin trinitrite (GTN), and prostaglandin E_1 (PGE$_1$), observing carotid arterial blood flow by the Doppler's methods in an effort to compare their effects on cerebral circulation and metabolism.

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Materials and Methods

Included in the present study were 45 patients who underwent lower abdominal surgery in Nippon Medical School Hospital. The patients were classified to class I or II in ASA physical status. They were divided into three groups, 15 patients per group, according to hypotensive agents used during anesthesia, such as TMP, GTN and PGE$_1$. There was no significant difference among the three groups with respect to age, distribution of sex, body weight and mean arterial pressure at preoperative period (table 1).

Anesthesia was induced by injecting 5 mg·kg^{-1} of thiamylal sodium and 1 mg·kg^{-1} of suxamethonium without making any premedication. Anesthesia was maintained by inhalation of 66% nitrous oxide supplemented by 0.5 to 1.5 MAC of enflurane. Muscle relaxation was facilitated with intra-

Table 1. age, sex, body weight, mean arterial pressure at preoperative state

	TMP group	GTN group	PGE₁ group
age	50.0 ± 14.3	50.3 ± 9.6	47.7 ± 10.4
sex	♂3 ♀12	♂5 ♀10	♂4 ♀11
B.W. (kg)	52.6 ± 7.9	54.4 ± 9.8	57.5 ± 11.5
MAP (mmHg)	85.5 ± 10.3	86.6 ± 6.2	83.2 ± 11.1

(Mean ± SD)

B.W.: body weight,
MAP: mean arterial pressure
• There was no significant difference among the three groups.

venous pancuronium bromide. The end-tidal CO_2 concentration was continuously monitored using a capnometer (Datex Normocap). Respiration was controlled by an anesthesia ventilator, so that Pa_{CO_2} was maintained between 35 and 40 mmHg.

A catheter was introduced upward into the left internal jugular vein, being positioned at jugular bulb to withdraw the blood sampling which came from brain. Another catheter was also inserted into a radial artery for monitoring of arterial blood pressure and for sampling arterial blood.

Two techniques were adopted to determine cardiac output. The one was the thermodilution method; a 7F baloon chip catheter with thermister (Edwards Co. Ltd) was inserted into a pulmonary artery through the right internal jugular vein in 6 of 15 patients in each group. This catheter was also used to collect take the mixed venous blood, and to record central venous pressure and pulmonary arterial pressure. The changes of blood temperature after injection of 5 ml of 0°C 5% gulucose solution were input into a Computer, Edwards Co. Ltd Type SAT-1, and the cardiac output was automatically calculated. The second was the impedance method; electrodes were applied on the chest and neck, leading the changes of impedance produced by stroke volume into a machine, BOMED Co. Ltd NCCOM3, in the remaining 9 patients.

The parameters, such as mean arterial pressure (MAP), heart rate (HR), pulmonary arterial wedge pressure (PAWP), central venous pressure (CVP), were measured. Cardiac index (CI), systemic vascular resistant index (SVRI), pulmonary vascular resistant index (PVRI) and oxygen consumption ($\dot{V}o_2$), were calculated from values obtained above.

The right common carotid arterial blood flow was determined with Nihon Kohden QFM system 1000, which was originally designed to measure alterations of vascular section area and blood flow velocity simultaneously. The blood flow was calculated by the integration of the velocity multiplied by the caliber of the artery. The caliber was measured by the ultrasonic pulse echo trcking method and the velocity by Doppler's ultrasonic method. For the calculation of cerebral blood flow, the ratio of the common carotid artery, internal carotid artery, external carotid artery and vertebral artery was assumed to be 1.9: 1.0: 0.9: 0.9[4]. The measurements were made by a fixed investigator, because this technique allowed the fluctuation of values by the probe direction. The mean value of 5 measurements after discarding the highest and lowest values of 7 times was adopted as a representative.

The subarachnoid cavity was punctured at $L_{3/4}$ level in 6 out of 15 patients in each group, facilitating placement of a fine catheter to record continuously the cerebrospinal fluid pressure (CSFP). Standard point for the pressure determination was set on mid axillar line at recumbent position.

The arterial, central venous, pulmonary arterial and CSFP were recorded on a polygraph, Nihon Kohden life Scope 11. Blood gas analysis and the determination of concentrations of lactate (L) and pyruvate (P) were conducted using withdrawn blood from radial artery, jugular bulb and pulmonary artery. Cerebral oxygen consumption ($CMRO_2$) were calculated from the product of the calculated CBF and the arterial-internal jugular blood oxygen content gradient. Cerebral perfusion pressure (CPP) was determined as difference between MAP and

Table 2. Parameters representing systemic and pulmonary circulation

		Control	Hypotension	Recovery	n
MAP (mmHg)	TMP	85 ± 6	62 ± 5*	86 ± 5	
	GTN	84 ± 5	63 ± 2*	82 ± 4	15
	PEG$_1$	83 ± 7	63 ± 3*	84 ± 8	
HR (beats·min^{-1})	TMP	73 ± 5	72 ± 5	75 ± 6	
	GTN	76 ± 4	76 ± 6	81 ± 7	15
	PEG$_1$	74 ± 6	84 ± 6*	78 ± 6	
MPAP (mmHg)	TMP	14 ± 3	11 ± 3	15 ± 3	
	GTN	16 ± 4	12 ± 4	13 ± 4	6
	PEG$_1$	14 ± 3	12 ± 3	13 ± 4	
PAWP (mmHg)	TMP	10 ± 3	7 ± 2*	9 ± 2	
	GTN	9 ± 2	6 ± 2*	9 ± 2	6
	PEG$_1$	9 ± 2	8 ± 2*	8 ± 3	
CVP (mmHg)	TMP	8 ± 2	6 ± 2*	8 ± 3	
	GTN	9 ± 3	7 ± 3*	9 ± 3	6
	PEG$_1$	8 ± 2	7 ± 2	7 ± 3	
CI (l·min^{-1}·m^2)	TMP	2.8 ± 0.4	2.2 ± 0.4*	2.6 ± 0.3	
	GTN	2.7 ± 0.2	2.2 ± 0.1*	2.5 ± 0.3	15
	PEG$_1$	2.9 ± 0.4	3.3 ± 0.4*	3.1 ± 0.4	
SVRI (dyne·sec^{-1}·cm^{-5}·m^{-2})	TMP	2240 ± 133	1649 ± 175*	2194 ± 82	
	GTN	2198 ± 511	1796 ± 400*	2292 ± 350	6
	PEG$_1$	2173 ± 520	1433 ± 252*	1991 ± 458	
PVRI (dyne·sec^{-1}·cm^{-5}·m^{-2})	TMP	144 ± 17	113 ± 19*	153 ± 14*	
	GTN	185 ± 57	162 ± 44*	178 ± 28	6
	PEG$_1$	146 ± 47	127 ± 21	148 ± 14	
$\dot{V}_{O_2}$I (ml·min^{-1}·m^{-2})	TMP	80 ± 10	73 ± 8*	82 ± 9	
	GTN	69 ± 16	66 ± 12	66 ± 14	6
	PEG$_1$	73 ± 30	68 ± 19	86 ± 25	

*$P < 0.05$ (Mean ± SD)

MAP: mean arterial pressure, HR: heart rate,
MPAP: mean pulmonary arterial pressure,
PAWP: pulmonary artery wedge pressure, CVP: central venous pressure,
CI: cardiac index, SVRI: systemic vascular resistant index,
PVRI: pulmonary vascular resistant index, $\dot{V}_{O_2}$I: $\dot{V}_{O_2}$ index

CVP. Cerebrovascular resistance (CVR) was calculated by dividing CPP by CBF. The weight of the brain was assumed as 1,500 g.

The control values were obtained when the cardiovascular status had been stabilized after induction of anesthesia. Hypotension was gently induced by administration of the hypotensive agents as the mean arterial blood pressure delined to 60 mmHg at a rate 10 mmHg for a minute. The blood pressure was maintained between 60 and 65 mmHg for 20 min. The values were obtained at the end period of hypotension. And same items were observed at 30 min after the infusion of hypotensive agents were ceased. The initial and maintenance doses of hypotensive drugs needed to achieve desired blood pressure were 50–80 and 10–20 mcg·kg^{-1}·min^{-1} for TMP, and 5–8 and 2–4 mcg·kg^{-1}·min^{-1} for GTN, and 0.15–0.25 and

Table 3. Circulatory and metabolic values concerning brain and CSFP

		Control	Hypotension	Recovery
CBF $(ml \cdot min^{-1})$	TMP	1121 ± 186	899 ± 163*	1041 ± 153*
	GTN	1079 ± 217	933 ± 215*	1012 ± 272*
	PEG_1	1109 ± 190	1303 ± 260*	1186 ± 270
radial artery-internal jugular vein O_2 content gradient $(ml \cdot dl^{-1})$	TMP	3.9 ± 1.0	4.2 ± 1.0	3.6 ± 1.1
	GTN	3.8 ± 0.9	4.1 ± 0.8	3.7 ± 1.0
	PEG_1	3.8 ± 1.0	3.4 ± 1.1	3.6 ± 1.2
CMR O_2 $(ml \cdot min^{-1})$	TMP	43.6 ± 8.6	37.4 ± 8.0*	39.3 ± 10.0*
	GTN	40.8 ± 7.1	38.4 ± 7.0	39.3 ± 8.4
	PEG_1	42.2 ± 8.7	44.1 ± 10.0	42.5 ± 10.0
CPP $(mmHg)$	TMP	69.7 ± 5.2	52.2 ± 2.2*	70.1 ± 6.5
	GTN	70.4 ± 3.6	51.3 ± 1.5*	66.9 ± 9.5*
	PEG_1	67.3 ± 2.3	51.3 ± 1.1*	65.4 ± 3.3
CVR $(mmHg \cdot ml^{-1} \cdot min^{-1} \cdot 100g^{-1})$	TMP	0.93 ± 0.10	0.87 ± 0.09*	0.96 ± 0.15
	GTN	0.98 ± 0.09	0.82 ± 0.15*	0.99 ± 0.20
	PEG_1	0.91 ± 0.05	0.59 ± 0.07*	0.87 ± 0.11
internal jugular vein Lactate $(mg \cdot dl^{-1})$	TMP	19.8 ± 3.6	22.0 ± 3.0	22.7 ± 2.8*
	GTN	19.0 ± 2.8	21.1 ± 2.5	21.2 ± 3.0
	PEG_1	19.7 ± 2.8	22.3 ± 3.6	22.5 ± 3.1
internal jugular vein L/P	TMP	17.8 ± 2.0	18.8 ± 1.5	20.8 ± 2.0*
	GTN	16.5 ± 1.5	17.8 ± 2.2	17.2 ± 2.1
	PEG_1	16.7 ± 1.6	18.2 ± 3.0	18.3 ± 2.8*
CSFP $(mmHg)$	TMP	14.1 ± 2.0	12.9 ± 1.8*	13.5 ± 2.5
	GTN	14.2 ± 2.3	15.3 ± 3.2*	14.1 ± 3.0
	PEG_1	14.1 ± 5.0	14.3 ± 4.9*	12.7 ± 5.9

$*P < 0.05$ (Mean ± SD, n = 15)

CBF: cerebral blood flow, $CMRO_2$: cerebral metabolic rate for O_2,
CPP: cerebral perfusion pressure, CVR: cerebral vascular resistance
L/P: Lactate/Pyruvate, CSFP: cereblo-spinal fluid pressure

0.05–0.10 $mcg \cdot kg^{-1} \cdot min^{-1}$ for PGE_1 respectively.

The values obtained were expressed as mean and standard deviations. The differences between the three groups were tested by analysis of variance. The differences between values obtained after administration of hypotensive drugs and pre-treatment controls in each group were assessed by Student's T-test. The statistical hypothesis was rejected if the probability was lower than 5%.
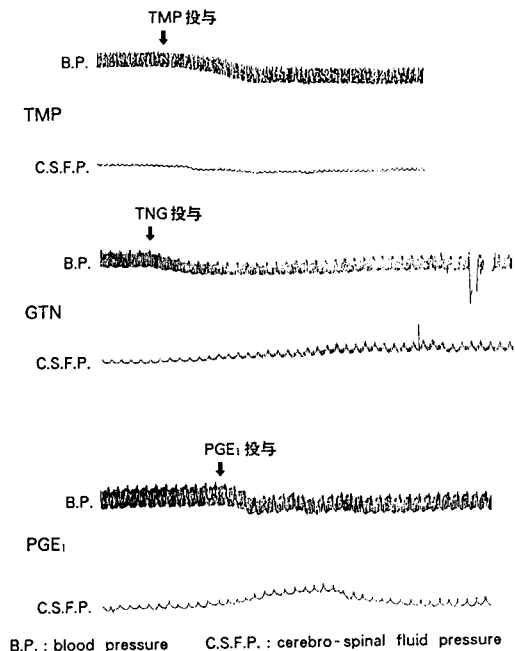
Results

Table 2 shows parameters representing systemic and pulmonary circulation. No dif-ference was observed in all values among the three groups at control period.

Most marked differences were noted with respect to cardiac output during induced hypotension. The CI decreased significantly both in the TMP and GTN group in compared with the values obtained at control period. On the contrary, the CI increased markedly in the PGE_1 group. MAP, PAWP, SVRI significantly decreased in compared with control values. However, no difference in these changes were found among the three groups. HR increased only in the PGE_1 group.

Cerebral circulatory and metabolic values and cerebrospinal fluid pressure before, dur-

TMP 投与
↓

B.P.

TMP

C.S.F.P.

TNG 投与
↓

B.P.

GTN

C.S.F.P.

PGE₁ 投与
↓

B.P.

PGE₁

C.S.F.P.

B.P. : blood pressure   C.S.F.P. : cerebro-spinal fluid pressure

Fig. 1. Typical tracings of CSFP are shown. In the TMP group, it decreased to 92% of the control value. But in the GTN and PGE_1 groups, it increased to 108 and 103% of each control value. The alterations of CSFP were biphasic in the PGE_1 group, showing a transient elevation and rapid recovery to the control value.

ing and after the hypotension were listed in table 3. All values at control period showed no difference among the three groups which received each agent. CBF reduced to 78 and 82% of control value in the TMP and GTN group, respectively, during induced hypotensive period, while it elevated to 111% of the control value in the PGE_1 group. The cerebral A-V oxygen content gradient remained unchanged throughout the study. The $CMRO_2$ decreased only in the TMP group during the hypotension period. The CPP declined concomitantly with BP in the three groups during the induced hypotension. Although CVR decreased significantly in all the three groups, the changes was largest in the PGE_1 group. However, no change was found in both L and L/P in the three groups during the hypotension period.

CSFP value spread considerably, namely from 8 to 18 mmHg (with mean of 14 mmHg) at control period. It decreased signif-

icantly to 92% of control value in the TMP group but increased significantly to 108 and 103% in the GTN and PGE_1 groups, respectively. The alterations of CSFP were biphasic in the PGE_1 group, showing a transient elevation and rapid recovery to control level. Typical tracings of CSFP are shown in figure 1.

Discussion

Induced hypotension has been conducted to minimize blood loss during surgical procedures. It is associated with some complications as Little[1] pointed out a higher mortality rate 30 years ago. However, the need for induced hypotension increased in the last decade because of the progress in microsurgery in which oozing of the blood disturbs surgical procedure extremely.

Few papers have been reported on the cerebral circulation and metabolism during induced hypotension clinically. In the present study, therefore, the author compared the effects of agents currently used to induce hypotension, TMP, GTN and PGE_1, on the circulation and metabolism in the brain.

Hypotension was induced by infusion of the three agents in the present study. Dose of each agent to induce and maintain hypotension at desired level was coincided with reports of many investigators[5-7].

There are many problems in determining CBF of anesthetized patients in a operation theater. Several techniques have been introduced for the quantitative measurement of CBF such as nitrous oxide method[8], xenon clerance method[9], Doppler method and so on.

The method adopted in the present study was a modified Doppler technique. This method was based on the computation of common carotid arterial blood flow from integrated velocity of the blood flow and caliber of the artery. CBF was calculated assuming that blood flow in the common, internal and external carotid arteries and vertebral artery is constant and distributed at the ratio previously reported[4]. This technique remained the problems of accuracy and reproducibility. However, the changes of
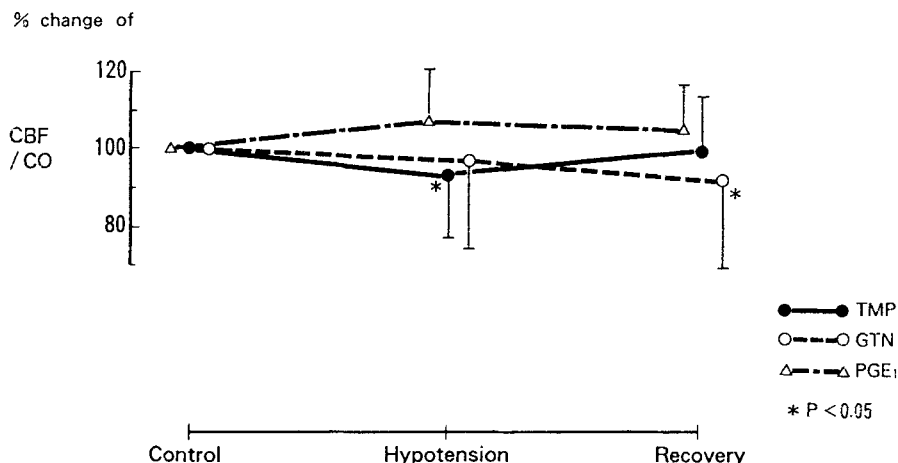
% change of

CBF : cerebral blood flow   CO : cardiac output

Fig. 2. The proportion of cerebral blood flow which accounts for cardiac output (CBF/CO) decreased to 90% in the TMP group, while it unchanged in the GTN and PGE$_1$ groups.

blood flow during this study could be appropriately evaluated by making measurements several times using a probe located in a fixed position and calculating the mean of several measurements. It has been reported that 1.1 MAC anesthesia with enflurane increases by 37% in CBF[10], the normal vale of which has documented as 50–60 ml·min^{-1}·100g^{-1} in intact man[8,11]. Therefore the CBF of 76 ± 10 ml·min^{-1}·100g^{-1} obtained at the control stage under the enflurane anesthesia was evaluated fairly acceptable.

Autoregulation of CBF may be disturbed by inhalational anesthetics, allowing significant fluctuations during induced hypotension by clinically utilized techniques[12]. In the present study, CBF decreased to 78 and 82% of the pre-treatment baseline in the TMP and GTN groups, respectively, and elevated to 111% in the PGE$_1$ group. The changes were almost proportional to those of cardiac output. The proportion of CBF to cardiac output was unchanged in the GTN and PGE$_1$ groups, while it was decreased in the TMP group during the hypotensive period as shown in figure 2.

There are controversies in the influence of PGE$_1$ on the cerebral circulation[13-16]. Mat-

sumae et al.[16] reported that CBF changed biphasically following the induction of hypotension, namely it increased under light hypotension and decreased under severe hypotension.

It is generally believed that intracranial pressure is closely related to CBF, being elevated by an increase of perfusion flow. However, cerebral blood flow and intracranial pressure do not always change in the same direction when vasodilative agents are used. Anticipated changes were observed in the TMP and PGE$_1$ groups. On the other hand a paradoxical change was noted in the GTN group. The increase in intracranial pressure associated with GTN, in spite of decrease in blood flow, would attribute to expansion of intracranial blood volume because of venous dilatation caused by GTN. CSFP in patients who received PGE$_1$ showed a biphasic pattern, an initial rise and a subsequent decline. The fact may suggest that the intracranial blood volume decreased after initial increase by arterial dilatation.

The analysis of oxygen concentration in the arterial and internal jugular venous blood concomitantly with the determination of CBF brings some informations on cerebral
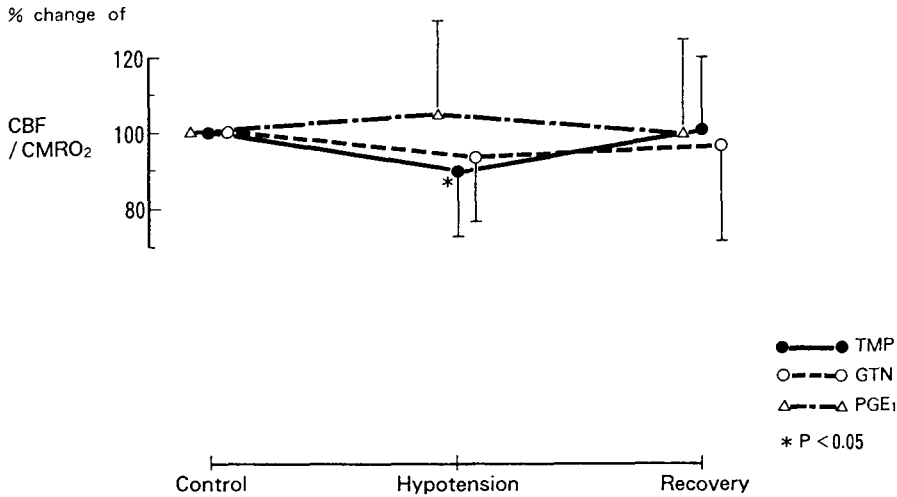
% change of

CBF : cerebral blood flow   CMRO2 : cerebral metabolic rate for O2
Fig. 3. The cerebral circulatory index (CBF/CMRO$_2$) was greatest for PGE$_1$, followed by GTN and TMP.

oxygen consumption[17]. CMRO$_2$ decreased significantly in the TMP group without changes in lactate concentration and L/P in internal jugular venous blood in the present study. CMRO$_2$ remained unchanged in the GTN and PGE$_1$ groups. Those results were similar to reports by other investigators[18,19]. The fact that CMRO$_2$ shows lesser changes than cerebral blood flow does seems to suggests that O$_2$ is extracted to a certain extent during hypotension. However, the most important is the relationship between oxygen supply and demand in the brain. The cerebral circulatory index proposed by Takeshita et al.[20] is a ratio of CBF to CMRO$_2$, representing the supply side of oxygen to the brain. The index declined in the TMP group during the induced hypotension as shown in figure 3.

All the above-mentioned findings were obtained with respect to blood circulation and metabolism in the whole brain. Further studies are requested on the local circulation and metabolism of the brain during induced hypotension[21].

In conclusion CBF decreased in patients with induced hypotension by TMP and GTN, while it increased in the PGE$_1$ group. Intracranial pressure elevated markedly in the GTN group and slightly in the PGE$_1$

group. CMRO$_2$ reduced slightly in the TMP group without other metabolic alterations. The results suggest that cerebral perfusion and metabolism might be affected during the induced hypotension using these three agents and that great caution will be needed to select hypotensive agent understanding patient condition.

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