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Prostaglandin E₁ and carbon dioxide reactivity during cerebral aneurysm surgery

The purpose of this study was to evaluate the effect of prostaglandin E₁ (PGE₁) on CO₂ reactivity during cerebral aneurysm surgery in 37 patients under neuroleptoanaesthesia (NLA). The patients were divided into two groups based on the timing of surgery (A: late surgery, B: early surgery). In the early surgery group, aneurysm surgery was performed within three days of subarachnoid haemorrhage (SAH) and in the late surgery group surgery was performed more than four days after SAH. Presurgical neurological status was worse in the early surgery group than in the late surgery group ($P < 0.01$). Local cerebral blood flow (LCBF) measurements were made using a thermal gradient blood flow meter. Hypotension was induced by PGE₁ administration at an initial dose of $0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and adjusted to maintain the mean arterial pressure (MAP) at about 70 mmHg. The CO₂ reactivity was calculated by the % change in LCBF divided by the change in PaCO₂ ($\% \Delta \text{LCBF} / \Delta \text{PaCO}_2$ ($\% \cdot \text{mmHg}^{-1}$)). LCBF, heart rate and mean arterial blood pressure were measured during and after PGE₁ infusion. Carbon dioxide reactivity was measured before, during and after PGE₁ administration. The LCBF did not change throughout the study but CO₂ reactivity was greater in Group A (before hypotension: $2.74 \pm 0.85 \%$ $\cdot \text{mmHg}^{-1}$, during hypotension: $2.54 \pm 0.73 \%$ $\cdot \text{mmHg}^{-1}$, after hypotension: $2.59 \pm 1.17 \%$ $\cdot \text{mmHg}^{-1}$) than in group B (before hypotension: $1.54 \pm 0.57 \%$ $\cdot \text{mmHg}^{-1}$, during hypotension: $1.56 \pm 0.59 \%$ $\cdot \text{mmHg}^{-1}$, after hypotension: $1.49 \pm 0.42 \%$ $\cdot \text{mmHg}^{-1}$) ($P < 0.01$). Outcome which was graded by

Glasgow Outcome Scale at discharge, was better in Group A ($P < 0.05$). There were close correlations between presurgical neurological status and outcome ($r_s = 0.743$ $P < 0.01$) and between presurgical neurological status and CO₂ reactivity before ($r_s = -0.558$, $P < 0.01$), during ($r_s = -0.636$, $P < 0.01$) and after hypotension ($r_s = -0.773$, $P < 0.01$). These findings suggest that PGE₁ maintains LCBF and CO₂ reactivity, and CO₂ reactivity and outcome are correlated closely with the presurgical neurological status.

Le but de cette étude était d'évaluer l'effet de la prostaglandine E₁ (PGE₁) sur la réactivité au CO₂ pendant une chirurgie pour anévrisme cérébral sous neuroleptanesthésie (NLA) chez 37 patients. Les patients étaient divisés en deux groupes selon le temps de la chirurgie (A : chirurgie tardive, B : chirurgie précoce). Dans le groupe avec chirurgie précoce, la chirurgie anévrysmale était faite en dedans de trois jours de l'hémorragie sous-arachnoïdienne (SAH) et dans le groupe avec chirurgie tardive, la chirurgie était faite plus de quatre jours après la SAH. L'état neurologique préchirurgical était pire dans le groupe avec chirurgie précoce que dans le groupe avec chirurgie tardive ($P < 0,01$). Les mesures du débit sanguin cérébral local (LCBF) étaient faites à l'aide d'un débitmètre sanguin à gradient thermique. L'hypotension était induite par l'administration de PGE₁ à une dose initiale de $0,1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ et ajustée afin de maintenir une tension artérielle moyenne (MAP) d'environ 70 mmHg. La réactivité au CO₂ était calculée par le pourcentage du changement de LCBF divisé par le changement de la PaCO₂ ($\% \Delta \text{LCBF} / \Delta \text{PaCO}_2$ ($\% \cdot \text{mmHg}^{-1}$)). Des mesures du LCBF, de la fréquence cardiaque et de la tension artérielle moyenne étaient faites pendant et après la perfusion de PGE₁. La réactivité au CO₂ était mesurée avant, pendant et après l'administration de PGE₁. Le LCBF n'a pas changé pendant toute la durée de l'étude mais la réactivité aux CO₂ était plus grande dans le groupe A (avant l'hypotension : $2,74 \pm 0,85 \%$ $\cdot \text{mmHg}^{-1}$, pendant l'hypotension : $2,54 \pm 0,73 \%$ $\cdot \text{mmHg}^{-1}$, après l'hypotension : $2,59 \pm 1,17 \%$ $\cdot \text{mmHg}^{-1}$) que dans le groupe B (avant l'hypotension $1,54 \pm 0,57 \%$ $\cdot \text{mmHg}^{-1}$, pendant l'hypotension $1,56 \pm 0,59 \%$ $\cdot \text{mmHg}^{-1}$, après l'hypotension $1,49 \pm 0,42 \%$ $\cdot \text{mmHg}^{-1}$) ($P < 0,01$). L'issue, évaluée au départ à l'aide de l'échelle de Glasgow sur l'issue («Glasgow Outcome Scale»), était meilleure dans le groupe A ($P < 0,05$). Il y avait

Key words

ANAESTHESIA TECHNIQUES: hypotensive;
BRAIN: blood flow;
PHARMACOLOGY: prostaglandin E₁.

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des corrélations étroites entre le statut neurologique préchirurgical et l'issue ($r_s = 0,743$, $P < 0,01$) et entre le statut neurologique préchirurgical et la réactivité au CO_2 avant ($r_s = -0,558$, $P < 0,01$), pendant ($r_s = -0,636$, $P < 0,01$) et après l'hypotension ($r_s = -0,773$, $P < 0,01$). Ces trouvailles suggèrent que la PGE_1 maintient le LCBF et la réactivité au CO_2 , et que la réactivité au CO_2 et l'issue sont en corrélation étroite avec l'état neurologique préchirurgical.

The optimal timing of operation for ruptured cerebral aneurysm remains controversial.¹ Many authors have demonstrated that in certain cases without significant neurological deficit or altered levels of consciousness, early operation may be well tolerated, with gratifying post-operative results and a low mortality rate.² During the first two weeks after subarachnoid haemorrhage (SAH) several events may affect the ability of the cerebral vasculature to react adequately. We previously reported that prostaglandin E_1 (PGE_1) maintained local cerebral blood flow (LCBF) during cerebral aneurysm surgery during deliberate hypotension.³ To evaluate the effect of PGE_1 on CO_2 reactivity, we studied CO_2 response during PGE_1 -induced hypotensive anaesthesia in patients with ruptured cerebral aneurysm surgery under neuroleptoanaesthesia (NLA) and the outcome of patients after early or late surgery was evaluated.

Methods

The protocol was approved by the subcommittee on human studies at the Osaka Police Hospital and informed consent was obtained from each patient or his appropriate relative. A detailed description of the methods has been given in a previous paper³ and will only be summarized here. Thirty-seven patients undergoing cerebral aneurysm clip ligation for ruptured cerebral aneurysm were evaluated. The patients were divided into two groups based on the timing of surgery after SAH. Group A consisted of 15 patients who were operated on more than four days after SAH (late surgery). Group B consisted of 22 patients who were operated on within three days after SAH (early surgery). The timing of operation was based on the clinical condition, aneurysm location and the medical condition of the patients. Subarachnoid haemorrhage was documented in all cases by bloody spinal tap and/or computerized tomographic scanning. Four vessel angiography was performed to confirm the presence of cerebral aneurysms. Patients with SAH were graded using the scale of Hunt and Kosnik⁴ which was recorded at the time of admission to the operating room. Outcome of patients was graded by Glasgow Outcome Scale at discharge.⁵ Patients received premedication with 0.5 mg atropine sulphate and 100 mg phenobarbitone *im* one hour before surgery. Anaesthesia

was induced with thiopentone ($4 \text{ mg} \cdot \text{kg}^{-1}$), fentanyl (0.1 mg), and pancuronium ($0.1 \text{ mg} \cdot \text{kg}^{-1}$) was used to facilitate tracheal intubation. Mechanical ventilation was started using 70% nitrous oxide in oxygen. Droperidol ($0.1 \text{ mg} \cdot \text{kg}^{-1}$) was administered *iv* after the trachea was intubated. Anaesthesia was maintained with fentanyl ($2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$) and N_2O (70%). A radial artery catheter aided continuous monitoring of arterial blood pressure as well as arterial blood sampling. A venous cannula was introduced into the femoral vein for the infusion of PGE_1 . Mean arterial pressure (MAP) and heart rate (HR) were also monitored. After the dura mater was opened, the probe of a thermal gradient blood flow meter (Biomedical Science Co., Ltd.) was placed on the middle frontal gyrus, 3–4 cm from the nearest point of intended brain retraction. The thermogradient blood flow meter used in this study is based on changes in heat conductivity of the tissue in response to altered blood flow. This thermal gradient is maximum when no blood is passing through the cerebral cortex (V_0). As cortical blood flow increases, the temperature difference decreases in proportion to the flow. The tissue blood flow (F) is calculated by the following formula from the electromotive force (V) of the thermocouple generated by temperature changes: $F = k(1/V - 1/V_0)$ in which k is a constant. From this formula, tissue blood flow (F) is obtained.⁶

Control measurements were made just before the start of PGE_1 administration. Then, $0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ of PGE_1 was administered and the dose was adjusted to maintain MAP at about 70 mmHg. The LCBF was measured continuously. The PGE_1 was discontinued at the completion of cerebral aneurysm clip ligation. Carbon dioxide reactivity was obtained 60 min after the start of PGE_1 and at 60 min after its discontinuation. To evaluate CO_2 reactivity the PaCO_2 was changed by increasing minute ventilation volumes.

Carbon dioxide reactivity values were obtained by dividing the value for the percentage of change in the LCBF by the value for the change in PaCO_2 , $\% \Delta \text{LCBF} / \Delta \text{PaCO}_2$ ($\% \cdot \text{mmHg}^{-1}$). Cerebral aneurysm clip ligation was performed by the same neurosurgeon in all patients.

Statistical analysis

The values are expressed as mean values $\pm$ SD. Statistical analysis of correlation between presurgical neurological status and Glasgow Outcome Scale was performed with the Spearman Rank test. Statistical analysis of presurgical neurological status and outcome between groups were performed with the Mann-Whitney U test. Statistical analysis of correlation between presurgical neurological status and CO_2 reactivity was performed with the Spearman Rank test. Comparison of MAP, HR, LCBF and CO_2 reactivity within and between groups was performed using

TABLE I Patients' backgrounds

No.	Age	M/F	Aneurysm location	NS	Outcome	Days after SAH
<i>Group A</i>						
1	56	M	MCA	I	I	14
2	68	F	IC	I	I	10
3	41	F	IC	I	I	13
4	50	F	AcomA	III	III	4
5	26	F	AcomA	II	I	5
6	80	M	AcomA	II	III	5
7	55	M	MCA	I	I	4
8	55	M	IC	I	I	5
9	44	F	IC	II	I	7
10	55	F	IC	I	I	4
11	21	M	AcomA	II	II	5
12	48	M	IC	II	I	10
13	44	M	IC	I	I	14
14	61	F	Basil	I	IV	21
15	57	M	MCA	I	I	18
mean	50.7					
SD	14.3					
<i>Group B</i>						
1	59	F	IC	II	I	2
2	48	M	MCA	III	III	0
3	48	F	AcomA	IV	III	0
4	76	F	AcomA	III	II	0
5	60	F	AcomA	IV	III	0
6	47	F	MCA	II	I	0
7	41	F	MCA	IV	V	0
8	81	F	AcomA	III	I	0
9	41	F	IC	I	I	3
10	26	F	MCA	II	I	3
11	73	F	MCA	IV	V	0
12	43	M	AcomA	III	I	0
13	48	F	AcomA	I	I	2
14	73	F	AcomA	II	III	1
15	43	M	MCA	II	III	1
16	63	F	AcomA	III	IV	0
17	78	F	IC	III	II	0
18	48	M	MCA	III	IV	0
19	50	F	IC	IV	V	0
20	40	M	MCA	IV	V	0
21	57	F	MCA	V	V	0
22	74	F	ACA	II	II	1
mean	55.3			†	*	
SD	14.8					

AcomA: anterior communicating artery, MCA: middle cerebral artery, IC: internal carotid artery, ACA: anterior cerebral artery, BASIL: basilar artery. NS: presurgical neurological status. Outcome was graded with Glasgow Outcome Scale. Presurgical neurological status was graded with Hunt and Kosnik Scale. * $P < 0.05$, † $P < 0.01$, compared with Group A.

two-way analysis of variance (ANOVA) and Bonferroni procedure. A $P < 0.05$ was considered statistically significant.

Results

Table I shows the demographic data of the patients studied. The presurgical neurological status was better in Group A than in Group B ($P < 0.01$), and the Glasgow Outcome Scale was also better in Group A ($P < 0.05$). The

changes in MAP, HR and LCBF are given in Table II. After the start of PGE₁ administration, MAP decreased immediately in both groups. This change persisted one hour after the discontinuation of PGE₁ administration. The LCBF did not change either during PGE₁ administration or after the discontinuation of PGE₁. Table III shows the changes in CO₂ reactivity just before the start of PGE₁ administration, 60 min after the start of PGE₁ administration and 60 min after its discontinuation. Carbon dioxide

TABLE II

	Before PGE ₁ start	During hypotension	PGE ₁ discontinuation
Group A			
MAP	111.7 ± 12.3	73.3 ± 5.1*	96.9 ± 11.5†
HR	82.4 ± 8.9	80.4 ± 7.4	81.9 ± 8
LCBF	56.4 ± 5.9	54.6 ± 9	58 ± 7.1
Group B			
MAP	103.1 ± 8.4	74.8 ± 4.3*	90.5 ± 10.9†
HR	81.1 ± 10.9	83.6 ± 9.5	82.7 ± 8.7
LCBF	49.5 ± 11.4	50.3 ± 13.2	49.3 ± 11.5

MAP (mmHg): mean arterial pressure. HR (min⁻¹): heart rate.

LCBF (ml⁻¹ · 100 g⁻¹ · min⁻¹): local cerebral blood flow.

PGE₁: prostaglandin E₁.

**P* < 0.01, †*P* < 0.05 compared with before PGE₁ start.

TABLE III CO₂ reactivity (%mm · Hg⁻¹)

Before PGE ₁ start	During hypotension	PGE ₁ discontinuation
Group A		
2.74 ± 0.85	2.54 ± 0.73	2.59 ± 1.17
Group B		
1.54 ± 0.57*	1.56 ± 0.59*	1.49 ± 0.42*

PGE₁: prostaglandin E₁.

**P* < 0.01 compared with Group A.

reactivity did not change during the study within groups. The CO₂ reactivity was greater Group A than in Group B throughout the study (*P* < 0.01). There was a close correlation between presurgical neurological status and CO₂ reactivity before (*r*s = -0.558, *P* < 0.01), during (*r*s = -0.636, *P* < 0.01) and after deliberate hypotension (*r*s = -0.773, *P* < 0.01) (Figure).

Discussion

In this study CO₂ reactivity was preserved during PGE₁-induced hypotension, but was greater in the late surgery group than in the early surgery group. Also, there was a close correlation between presurgical neurological status and CO₂ reactivity. We divided patients into two groups based on the timing of operation and evaluated the outcome.

The major issue of this study is the method of cerebral blood flow measurement. We used the thermal gradient blood flow meter to measure the LCBF. The advantages of this method are noninvasiveness and quick applicability at the time of operation. However, it is necessary to bear in mind that this method may not measure flow in deep structures and may correlate poorly with total flow.

FIGURE There was a close correlation between presurgical neurological status and CO₂ reactivity before, during and after deliberate hypotension.

Timing of operation for ruptured cerebral aneurysms remains controversial.^{7,8} It is reported that early aneurysm surgery in good risk patients is not associated with high mortality or morbidity rates,^{9,10} but delayed operation is still preferred especially in the presence of good neurological status.

The LCBF values in both groups were comparable with previous reports using other methods,^{11,12} and CO₂ reactivity values were in good agreement with the previous report in patients with aneurysms using a temperature-controlled thermoelectrical method.¹³

Continuous PGE₁ administration caused no change in LCBF. The administration of PGE₁ was discontinued at the completion of the clipping procedure, but the antihypertensive effects of this drug and its effect on the LCBF persisted for one hour. The MAP remained low for one hour after discontinuation of the drug. Goto *et al.*¹⁴ also reported a prolonged hypotensive effect of PGE₁ during general anaesthesia, although the blood concentration of PGE₁ declined to the pre-administration level within about ten minutes after the end of administration. The reason for the prolonged effects of PGE₁ is unexplained.

Clinical grading is of great prognostic value.¹⁵ Patients with ruptured cerebral aneurysms have poor outcomes in spite of the use of modern neuroanaesthetic methods and microsurgical techniques.¹⁶ The reason for this poor outcome has been the subject of much controversy. In this study, patients in the early surgery group had worse outcome than in the late surgery group and the outcome was correlated closely with the presurgical neurological status (Table I).

After SAH, patients present various clinical conditions

depending on the severity of bleeding. The most important problems are disturbance of the autoregulatory function of blood flow to vital organs.¹⁷ Our patients had recent attacks of SAH. They may be more susceptible to cerebral blood flow reduction during hypotension than normal.¹⁸ Using the intraarterial ¹³³Xenon injection method, Ishii reported that impairment of autoregulation was correlated with the clinical status, cerebral blood flow and vasospasm.¹⁹ Heilbrun *et al.* reported that autoregulation was impaired but without verifiable relation to clinical conditions or angiographic vasospasm.²⁰

In our patients, CO₂ reactivity did not change during PGE₁ administration or after its discontinuation in either group. However, CO₂ reactivity was greater in Group A than in Group B ($P < 0.01$). Hyperventilation is recommended to reduce cerebral blood flow and cerebral blood volume in patients with brain protrusion and it is necessary to preserve CO₂ reactivity during induced hypotension. Even in severe cerebral apoplexy, CO₂ responsiveness is totally or partly preserved,²¹ but in an animal study, Artru reported that CO₂ responsiveness was abolished during hypotension induced with trimethaphan or sodium nitroprusside.²² The neurological status was greater in Group A patients than in Group B ($P < 0.01$). Anaesthetic agents affect cerebral blood flow. We used NLA for anaesthetic maintenance, because although fentanyl and droperidol may cause a decrease in the cerebral blood flow in experiments in dogs,²³ the combined administration of fentanyl and droperidol in human studies did not influence cerebral blood flow.²⁴

In hypotensive anaesthesia, induced by PGE₁, the effect on platelets should be taken into account, since PGE₁ is reported to inhibit platelet aggregation.²⁵ However, studies in humans suggest that PGE₁ does not inhibit platelet aggregation at clinical doses.²⁶

Using thermal gradient blood flow meter, we demonstrated that PGE₁ preserved LCBF and CO₂ reactivity. These results indicate that PGE₁ may be used to induce hypotension in cerebral aneurysm surgery.

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