Carbon dioxide reactivity and local cerebral blood flow during prostaglandin E₁- or nitroglycerine-induced hypotension

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The aims of this randomized study were to determine the effect of prostaglandin-(PGE₁) or nitroglycerine-(TNG) induced hypotension on local cerebral blood flow (LCBF) and carbon dioxide reactivity during isoflurane anaesthesia in 20 patients after subarachnoid haemorrhage (SAH) scheduled for aneurysm clip ligation. Mean arterial blood pressure decreased immediately, after giving either PGE₁ or TNG. The LCBF, measured using a thermal gradient blood flowmeter, was unchanged after PGE₁, while the LCBF increased after TNG infusion (control; 47.6 ± 10.0 , 60 min after infusion; 55.1 ± 6.5 ($P < 0.05$), before clipping; 55.5 ± 7.8 ($P < 0.05$)) but returned to control values after its discontinuation. Carbon dioxide reactivity, calculated from $\% \Delta \text{LCBF} / \Delta \text{PaCO}_2$, was unchanged during PGE₁- or TNG-induced hypotension (PGE₁; 2.13 ± 0.9 , 2.48 ± 0.68 and $2.31 \pm 0.79\%$ /mmHg for before, during and after hypotension respectively) (TNG; 2.08 ± 0.68 , 2.17 ± 0.64 and $2.02 \pm 0.69\%$ /mmHg for before, during and after hypotension respectively). Carbon dioxide reactivity correlated with presurgical neurological status ($r_s = -0.7$, -0.648 and -0.458 for before, during and after hypotension respectively) and the initial LCBF ($r_s = -0.605$). These results suggest that both PGE₁ and TNG are useful drugs for induced hypotension for cerebral aneurysm surgery, because neither decreased LCBF.

Key words

ANAESTHETIC TECHNIQUE: hypotension;
BRAIN: carbon dioxide tension;
HORMONES: prostaglandin E₁;
PHARMACOLOGY: nitroglycerine.

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Cette étude randomisée a pour objectifs de déterminer les effets de l'hypotension produite par la prostaglandine (PGE₁) ou par la nitroglicérine (TNG) sur le débit sanguin local (DSCL) et la réactivité au dioxyde de carbone pendant l'anesthésie à l'isoflurane chez 20 patients souffrant d'hémorragie subarachnoïdienne (HSA). La pression artérielle moyenne baisse immédiatement, après l'administration de PGE₁ ou de TNG. Le DSCL mesuré à l'aide d'un débitmètre à gradient thermique demeure in-changé après PGE₁, mais augmente après la perfusion de TNG (contrôle $47,6 \pm 10,60$ min après le début de la perfusion; $55,1 \pm 6,5$ ($P < 0,05$)) mais retourne aux valeurs de contrôle après l'arrêt de la perfusion. La réactivité au dioxyde de carbone calculée à partir de $\% \Delta \text{DSCL} / \Delta \text{PaCO}_2$ demeure in-changée durant l'hypotension induite par PGE₁ ou TNG. (PGE₁: $2,13 \pm 0,9$, $2,48 \pm 0,68$ et $2,31 \pm 0,79$ %/mmHg valeurs respectives mesurées avant, pendant et après l'hypotension, TNG: $2,08 \pm 0,68$, $2,17 \pm 0,64$ et $2,02 \pm 0,69$ %/mmHg valeurs respectives mesurées avant, pendant et après l'hypotension.) La réactivité au dioxyde de carbone est en corrélation avec le status neurologique pré-chirurgical. Ces résultats suggèrent que les deux drogues PGE₁ et NTG sont utiles pour l'hypotension provoquée en chirurgie de l'anévrisme cérébral parce qu'aucune des deux ne diminue le DSCL.

Induced hypotension during cerebral aneurysm surgery may reduce the risk of premature rupture, and facilitate the surgical procedure.^{1,2} Patients after subarachnoid haemorrhage (SAH) have disturbed cerebral vascular responses,³ and reduced cerebral blood flow secondary to SAH has been well documented in recent years.⁴ In previous studies, we reported that prostaglandin E₁ (PGE₁) maintained local cerebral blood flow (LCBF) and carbon dioxide reactivity,⁵ and that trimethaphan decreased cerebral blood flow during cerebral aneurysm surgery.⁶ The purpose of this study was to compare the effects of PGE₁ or nitroglycerine (TNG) on carbon dioxide reactivity

and local cerebral blood flow during isoflurane anaesthesia.

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 their relative. Twenty patients undergoing craniotomy for cerebral aneurysm clipping were studied. All patients had had a recent episode of subarachnoid haemorrhage (SAH), but were otherwise without any known cardiovascular, pulmonary, or other serious disease and were scheduled for clipping of the cerebral aneurysm. They were randomly assigned to one of two groups on a set rotational basis for the choice of agent used to induce hypotension. Hypotension was induced with either PGE₁ ($n = 10$) or TNG ($n = 10$). The diagnosis of SAH was confirmed by computerized tomography, four vessel cerebral angiography and lumbar puncture. Presurgical neurological status was graded with Hunt and Kosnik scale⁷ which is defined as follows: grade 0—unruptured aneurysms, grade I—asymptomatic, or minimal headache and slight nuchal rigidity, grade Ia—no acute meningeal or brain reaction, but with fixed neurological deficit, grade II—moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy, grade III—drowsiness, confusion or mild focal deficit, grade IV—stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity, and vegetative disturbances, grade V—deep coma, decerebrate rigidity, moribund appearance. Outcome was graded by the Glasgow Outcome Scale (GOS) at discharge by two independent neurosurgeons.⁸ The GOS is defined: grade I—good recovery, grade II—moderate disability, grade III—severe disability, grade IV—vegetative state, grade V—death.

Angiographic cerebral vasospasm was evaluated with cerebral angiography on the fifth to seventh day after surgery and was graded as: non-spasm (N), local vasospasm (L), global vasospasm (G).

All patients were given atropine, 0.5 mg *im* and phenobarbitone 100 mg *im* for premedication. On arrival in the operating room, an intravenous infusion was begun for drug and fluid administration. A catheter was inserted into the radial artery for blood pressure monitoring and blood gas analysis. Anaesthesia was induced with thiopentone 4 mg · kg⁻¹ *iv* supplemented with fentanyl 0.1 mg *iv* and isoflurane (inspired concentration 1–2.5%). Pancuronium 0.1 mg · kg⁻¹ was given to facilitate tracheal intubation. After tracheal intubation, mechanical ventilation was employed with a gas mixture of 50% nitrous oxide in oxygen to maintain PaCO₂ values at about 5.3 kPa. Anaesthesia was maintained with isoflurane (inspired concentration 1–1.5%). End tidal concentration of isoflu-

rane was monitored with a mass spectrometer (Hewlett Packard, M1025A, USA). All patients were operated upon in the horizontal supine position. A venous cannula was introduced into either the femoral vein or cubital vein for the infusion of hypotensive agents. After the dura mater was opened, the probe of a thermal gradient blood flow meter (Biomedical Science Co, Tokyo) was placed on the middle frontal gyrus, away from the point of intended brain retraction.

The measurement of flow by the thermal gradient blood flow meter used in this study is based on the change in heat conductivity of the tissue in response to the altered blood flow. The 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 LCBF is calculated by the following formula from the output (V) of the thermocouple generated by temperature changes: $LCBF = k(1/V - 1/V_0)$ in which k is a constant. From this formula, tissue blood flow is obtained.^{9,10}

Carbon dioxide reactivity was obtained by dividing the percentage of change in the LCBF by the change in PaCO₂: % $\Delta LCBF / \Delta PaCO_2$ (% mmHg⁻¹). The PaCO₂ was changed by altering the minute ventilation of the ventilator. Arterial blood sampling as obtained before and after the changes of ventilator settings and PaCO₂ was measured immediately by the automatic blood gas analyzer (Corning, USA).

Control measurements of LCBF, MAP, HR and carbon dioxide reactivity were made prior to the administration of hypotensive agents. Initially, PGE₁ or TNG was administered in a dose of 0.1 mg · kg⁻¹ · min⁻¹ and the dose was then adjusted to maintain the MAP at about 60 mmHg. Infusion of hypotensive agent was discontinued at the completion of cerebral aneurysm clipping. The LCBF, MAP, HR were measured, before the start of drug administration (T_0), at 10, 30, 60 min after the start of hypotensive drug infusion (T_1 , T_2 , T_3), before aneurysm clipping (T_4) and at 10, 30, 60 min after the end of drug infusion (T_5 , T_6 , T_7 respectively). Carbon dioxide reactivity was evaluated prior to the hypotensive drug infusion, 60 min after the start of infusion, and at 60 min after the end of infusion.

Statistic analysis

Values are expressed as mean $\pm$ standard deviation (SD). Statistical analysis of outcome and the incidence of vasospasm after surgery between groups was performed with the Mann-Whitney U test. Statistical analyses of haemodynamic changes, LCBF and carbon dioxide reactivity within and between groups were performed with two-way analysis of variance and Bonferroni correction. The correlation between presurgical neurological status

TABLE I Patients' backgrounds

	No.	Age	Sex	Aneurysm location	Neurological status	Outcome scale	Spasm
PGE ₁	1	48	F	IC	I	I	N
	2	65	M	A com A	II	I	N
	3	40	M	A com A	IV	IV	G
	4	56	M	MCA	II	III	L
	5	52	F	A com A	III	III	G
	6	38	F	A com A	II	I	N
	7	45	F	IC	I	I	N
	8	40	M	A com A	IV	IV	G
	9	65	F	IC	I	I	N
	10	75	M	MCA	I	I	N
	Mean	52.4					
TNG	SD	12.6					
	1	51	M	IC	IV	IV	G
	2	65	M	IC	III	IV	L
	3	43	F	IC	IV	IV	G
	4	68	M	A com A	I	I	N
	5	54	F	MCA	II	I	N
	6	54	M	A com A	II	I	N
	7	50	M	Basil	I	I	N
	8	75	F	A com A	II	II	N
	9	64	F	MCA	III	III	L
	10	45	M	A com A	II	II	L
	Mean	56.9					
	SD	10.5					

Acom A: anterior communicating artery; IC: internal carotid artery; MCA: middle cerebral artery; Basil: basilar artery; Neurological status was graded by Hunt and Kosnik scale; Glasgow Outcome scale: I—good recovery, II—moderate disability, III—severe disability, IV—persistent vegetative state, V—death; Spasm: non-spasm (N), local spasm (L), global spasm (G).

Classification of patients with intracranial aneurysms according to surgical risk

Grade	Criteria
0	Unruptured aneurysm.
I	Asymptomatic, or minimal headache and slight nuchal rigidity.
Ia	No acute meningeal or brain reaction, but with fixed neurological deficit.
II	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy.
III	Drowsiness, confusion, or mild focal deficit.
IV	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity, and vegetative disturbances.
V	Deep coma, decerebrate rigidity, moribund appearance.

(Clin Neurosurg 1974; 21: 80).

and outcome, between presurgical neurological status and carbon dioxide reactivity and between presurgical neurological status and LCBF before drug infusion were performed with Spearman Rank test. Values of $P < 0.05$ were regarded as statistically significant.

Results

Patients studied included five men and five women in the PGE₁ group, and six men and four women in TNG group. They ranged in age from 38–75 yr (mean 52.4 + 12.6) (PGE₁ group) and from 43–75 yr (mean 56.9 + 10.5) (TNG group) (Table I). There were no differences in age

or outcome between groups. Angiographic cerebral vasospasm after surgery was seen in four patients (local spasm: one patient, and global spasm: three patients) in the PGE₁ group and in five patients (local spasm: three patients, and global spasm: two patients) in the TNG group. The incidence of cerebral vasospasm after surgery was not different between groups. There was a close correlation between Hunt and Kosnik Scale and outcome ($r_s = 0.897$, $P < 0.01$). After the start of PGE₁ or TNG administration, MAP decreased immediately and remained stable throughout the infusion, but PGE₁-induced hypotension persisted for one hour after its discontinuation. There

TABLE II

		During infusion					Post-infusion		
	Pre-infusion	10 min	30 min	60 min	Preclipping	10 min	30 min	60 min	
MAP (mmHg)									
PGE ₁	114.1 ± 13.2	71.4 ± 12.9**	65.9 ± 11.2**	69.1 ± 17.3**	66.6 ± 13.3**	82.7 ± 5.4**	84.5 ± 7.2**	99.6 ± 11.9**	
TNG	105.8 ± 18.2	67.3 ± 5.6**	66.7 ± 6.3**	65.9 ± 6.7**	64.9 ± 6.7**	92.1 ± 8.8*	100 ± 7.1	104.3 ± 8.4	
HR (min ⁻¹)									
PGE ₁	82.4 ± 7.2	84.1 ± 11.1	84.3 ± 8.6	86.2 ± 4.0	89.2 ± 6.0	86.3 ± 6.4	87.1 ± 6.4	84.9 ± 5.4	
TNG	80.2 ± 11.9	80.1 ± 11.9	82.7 ± 11.6	82.6 ± 10.1	84.8 ± 11.2	83.1 ± 7.8	80.8 ± 9.4	84 ± 12.0	
LCBF (ml · 100 g ⁻¹ · min ⁻¹)									
PGE ₁	50.6 ± 9.5	52.4 ± 9.5	52 ± 12.1	51.6 ± 9.7	49.4 ± 12.1	53.2 ± 13.8	49 ± 9.8	47.9 ± 7.9	
TNG	47.6 ± 10.0	48.2 ± 9.5	51 ± 10.3	55.1 ± 6.5*	55.5 ± 7.8*	52.1 ± 7.5	48.9 ± 8.8	47.3 ± 7.9	
PaCO ₂ (mmHg)									
PGE ₁	35.7 ± 8.6			35.8 ± 7.8				37.9 ± 7.5	
TNG	36.7 ± 5.1			34.7 ± 7.3				37.4 ± 7.3	

Mean ± SD. ***P* < 0.01. **P* < 0.05.

TABLE III Carbon dioxide reactivity (%/mmHg)

	Pre-infusion	60 min after infusion	60 min after discontinuation
PGE ₁			
Carbon dioxide			
– reactivity	2.13 ± 0.9	2.48 ± 0.68	2.31 ± 0.79
– ΔPaCO ₂ (mmHg)	10.5 ± 2.3	10.9 ± 2.9	10.7 ± 1.8
– ΔLCBF (ml · 100 g ⁻¹ · min ⁻¹)	10.6 ± 2.6	13.1 ± 4.6	11.3 ± 4.5
TNG			
Carbon dioxide			
– reactivity	2.08 ± 0.68	2.17 ± 0.64	2.02 ± 0.69
– ΔPaCO ₂ (mmHg)	9 ± 2.3	11.3 ± 6	10.5 ± 3.8
– ΔLCBF (ml · 100 g ⁻¹ · min ⁻¹)	8.7 ± 4.7	11.7 ± 4.9	9.4 ± 4.4

Mean ± SD

were no differences in HR in either group (Table II). Carbon dioxide reactivity did not change within and between groups (Table III).

There was a close correlation between presurgical neurological status and initial cerebral blood flow (Figure 1) (*rs* = -0.605, *P* < 0.01).

The LCBF did not change in the PGE₁ group. However, in the TNG group, LCBF increased at 60 min after the infusion (*P* < 0.05) but it had returned to the preinfusion value after the discontinuation of TNG (Figure 2).

There was a close correlation between presurgical neurological status and carbon dioxide reactivity (before deliberate hypotension: *rs* = -0.7, *P* < 0.01, during deliberate hypotension: *rs* = -0.648, *P* < 0.01, after deliberate hypotension: *rs* = -0.458, *P* < 0.05) (Figure 3).

Discussion

A primary goal of the anaesthetic management of patients undergoing cerebral aneurysm surgery is to reduce the risk

of premature rupture of the aneurysms by careful maintenance of its transmural pressure. Induced hypotension was used to control the transmural pressure. But it can pose the risk of brain ischaemia if used in patients with cerebral arterial vasospasm, disrupted cerebral autoregulation. In this study, LCBF was increased 60 min after the start of the TNG infusion while with PGE₁ LCBF was maintained throughout surgery. Carbon dioxide reactivity was maintained with both PGE₁ and TNG during cerebral aneurysm clipping and showed a close correlation with presurgical neurological status (Hunt and Kosnik Scale).

A thermal gradient blood flow meter was employed to estimate LCBF. The major problem with this measurement of LCBF has been that it may fail to measure the flow in deep structures and may correlate poorly with total flow. The carbon dioxide reactivity values in this study were in good agreement with those of previous reports on cerebral aneurysm patients using a thermal conductivity probe for the measurement of cerebral blood flow.^{11,12}

FIGURE 1 Correlation between presurgical neurological status (Hunt and Kosnik Scale) and local cerebral blood flow before induced hypotension.

FIGURE 2 PGE₁ did not change local cerebral blood flow but TNG increased local cerebral blood flow at 60 min after the start of agent ($P < 0.05$). Preinfusion (T_0), 10 min, 30 min, 60 min after start of agent (T_1 , T_2 , T_3), preclipping (T_4), 10 min, 30 min, and 60 min after its discontinuation (T_5 , T_6 , T_7 respectively).

Cerebral vasoconstriction that results from hypocapnia causes a reduction of cerebral blood flow. However, so long as mean arterial blood pressure is maintained at nearly normal levels there is no evidence that hypocapnia of the degree used clinically affects the brain adversely. Artru *et al.* reported that combining hypocapnia with hypotension causes considerable cerebral blood flow disturbance.¹³

Decreased PaCO_2 results in the reduction of cerebral

FIGURE 3 Correlation between presurgical neurological status (Hunt and Kosnik Scale) and carbon dioxide reactivity before, during and after induced hypotension.

blood flow and cerebral blood volume and hence the reduction of increased intracranial pressure. Voldby *et al.* studied carbon dioxide reactivity systematically in 29 patients during hyperventilation within the first 13 days after aneurysm rupture. They reported that in all patients, a decrease in cerebral blood flow of 1 to 4% per millimeter of mercury of PaCO_2 reduction was found regardless of the clinical conditions, and that cerebral vascular reactivity to hypocapnia was well preserved in ruptured cerebral aneurysm patients. They concluded that the severe impairment was associated with cerebral ischaemia.¹⁴ In our study, carbon dioxide reactivity was not affected by the mild hypotension induced by PGE₁ or TNG and there was a close correlation between presurgical neurological status (Hunt and Kosnik Scale) and carbon dioxide reactivity.

The safety of systemic hypotension during cerebral aneurysm surgery depends on preservation of adequate cerebral blood flow. It is reported that there is a global decrease in cerebral blood flow in patients with SAH.^{4,15} And these patients frequently develop abnormal cerebrovascular reactivity and impaired autoregulation¹⁶ and they may be more susceptible to severe flow reductions during hypotension than normal individuals.⁴ We compared the effects of PGE₁ on LCBF and CO_2 reactivity with those of TNG. Nitroglycerine acts primarily by dilating the venous bed and decreasing the venous return to the heart,¹⁷ and has a short half-life and no important toxic metabolites. But low intracranial compliance is a contraindication to TNG use prior to dural opening.¹⁸ In this study, LCBF increased after the start of TNG but carbon dioxide reactivity did not change. The prostaglandins are a large family of naturally occurring substances with a variety of biological actions. The effect of PGE₁ on cerebral blood flow has been studied previously. But their reports have been contradictory.^{19,20} PGE₁ reduces blood pressure by

relaxing the vascular smooth muscle, mainly by dilatation of resistance vessels.²¹ Prostaglandin E₁ also dilates the systemic vascular smooth muscle.²² In this study, onset of hypotensive effect after PGE₁ infusion was very rapid while there was a residual hypotensive effect that persisted for one hour.

It has been reported that isoflurane also maintains cerebral blood flow during cerebral aneurysm surgery and is useful for cerebral aneurysm surgery.²³⁻²⁵

In conclusion, the present study demonstrated that PGE₁ maintained LCBF and carbon dioxide reactivity, while TNG increased LCBF during induced hypotension. Both TNG and PGE₁ are useful drugs for the induction of deliberate hypotension, because both of them did not decrease local cerebral blood flow throughout this study. The prolonged hypotensive effect of PGE₁ should be taken into consideration in clinical practice.

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