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Abstract

The basilar artery was exposed transclivally , and a vascular spasm was produced by topical application of a lysed erythrocyte solution. The maximum fall in the mean arterial blood pressure (MABP) after administering of 2 micrograms/ kgBW and 15 micrograms/ kgBW of PGI2, ranged from 35 to 45 mmHg and from 65 to 85 mmHg, respectively. The drop in MABP after an injection of papaverine hydrochloride (1.5 mg/ kgBW) was between 30 and 40 mmHg. If MABP did not fall, the vessel diameter did not change. Although papaverine elicited marked dilation of both normal and spastic basilar arteries, PGI2 did not dilate normal basilar arteries and produced only a slight dilation of spastic basilar arteries. Subarachnoid hemorrhage (SAH) was simulated by an intracisternal injection of fresh autologous arterial blood 3 days prior to experimentation. Changes in regional cerebral blood flow (rCBF) were measured by the heat clearance method, before and after an intravenous administration of either PGI2 or papaverine hydrochloride. Changes in rCBF fell into 3 categories: Type A, no change; Type B, a change which varied with the arterial blood pressure, and Type C, an increase rCBF despite systemic hypotension. Type A or B was observed in 17 out of 19 cats with SAH in which PGI2 was administered intravenously, and Type C was observed in only 2 cats. Thirteen untreated control cats produced a Type A or B response in 12, and Type C response in only one cat. There were no significant differences between the control and SAH groups. When 15-hydroperoxy-5, 8, 11, 13-eicosatetraenoic acid (15-HPETE) was infused, the same results prevailed. Papaverine hydrochloride increased rCBF either transiently or continuously in all cats. These results suggest that PGI2 dilates extracranial rather than intracranial vessels regardless of the presence or absence of cerebral vasospasm.

KEYWORDS: cerebral vasospasm, thromboxane A_2, prostaglandin I_2, papaverine

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PROSTACYCLIN AND THROMBOXANE IN CEREBRAL VASOSPASM : EFFECTS OF PROSTACYCLIN ON EXPERIMENTALLY-INDUCED CEREBRAL VASOSPASM

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Abstract. The basilar artery was exposed transclivally, and a vascular spasm was produced by topical application of a lysed erythrocyte solution. The maximum fall in the mean arterial blood pressure (MABP) after administering of 2 μg/kgBW and 15 μg/kgBW of PGI_2, ranged from 35 to 45 mmHg and from 65 to 85 mmHg, respectively. The drop in MABP after an injection of papaverine hydrochloride (1.5 mg/kgBW) was between 30 and 40 mmHg. If MABP did not fall, the vessel diameter did not change. Although papaverine elicited marked dilation of both normal and spastic basilar arteries, PGI_2 did not dilate normal basilar arteries and produced only a slight dilation of spastic basilar arteries. Subarachnoid hemorrhage (SAH) was simulated by an intracisternal injection of fresh autologous arterial blood 3 days prior to experimentation. Changes in regional cerebral blood flow (rCBF) were measured by the heat clearance method, before and after an intravenous administration of either PGI_2 or papaverine hydrochloride. Changes in rCBF fell into 3 categories : Type A, no change ; Type B, a change which varied with the arterial blood pressure, and Type C, an increase rCBF despite systemic hypotension. Type A or B was observed in 17 out of 19 cats with SAH in which PGI_2 was administered intravenously, and Type C was observed in only 2 cats. Thirteen untreated control cats produced a Type A or B response in 12, and Type C response in only one cat. There were no significant differences between the control and SAH groups. When 15-hydroperoxy-5, 8, 11, 13-eicosatetraenoic acid (15-HPETE) was infused, the same results prevailed. Papaverine hydrochloride increased rCBF either transiently or continuously in all cats. These results suggest that PGI_2 dilates extracranial rather than intracranial vessels regardless of the presence or absence of cerebral vasospasm.

Key words : cerebral vasospasm, thromboxane A_2, prostaglandin I_2, papaverine.

Delayed cerebral vasospasm after subarachnoid hemorrhage (SAH) following the rupture of an intracranial aneurysm frequently influences the patient's outcome (1). In spite of much research, the pathogenesis of vasospasm remains obscure. Prostacyclin (PGI_2) (2) generated in the vascular endothelium (3, 4) inhibits platelet aggregation and is one of the vasodilators of the peripheral circulation (5-8). PGI_2 also has been shown to possess vasodilatory action on cerebral circulation (8-11) and to be generated in the cerebral arteries (12, 13). Recently, it has been

shown that vasospasm induces morphological changes not only in the muscle layer but also in diffusely and severely damaged endothelium (14, 15). Some investigators have suggested that decreased synthesis of PGI_2 in cerebral vascular walls may be the cause of vasospasm (13, 16), and that PGI_2 may be a useful agent in the treatment of cerebral vasospasm (17). The purpose of the present study is twofold : 1) to elucidate the role of decreased PGI_2 synthesis in the etiology of vasospasm, and 2) to determine PGI_2's potential value in the treatment of cerebral vasospasm.

MATERIALS AND METHODS

Operative procedure. Intramuscular ketamine hydrochloride (2-0-chlorophenyl-2-methylaminocyclohexane hydrochloride) was given as an anesthetic (20 mg/kg) to 71 adult cats, weighing 2.5 kg to 4.5 kg, whose heads were then immobilized in a stereotaxic apparatus. After endotracheal intubation, the cats were paralyzed with intramuscular succinylcholine chloride (1 to 2 mg/kg), repeated if necessary, and maintained with a respirator (Respirator Model B_2 : Igarashi, Japan). Cannulators were introduced into the femoral artery for measurement of the mean arterial blood pressure (MABP) and the femoral vein for intravenous infusion. MABP was recorded with a pressure transducer (Statham SP-1405, USA) throughout the experiments, and blood gas values were measured frequently. Arterial blood gases were maintained within the following ranges : pH : 7.30-7.40 and PCO_2 : 32-40 mmHg.

The basilar artery was exposed transclivally under an operative microscope. After allowing for the hemostatic equilibrium to return, the dura was transected and the arachnoid membrane adjacent to the basilar artery was dissected carefully to avoid mechanically-induced spasm. If mechanical spasm was noted, the exposed basilar artery was bathed in isotonic saline (37 ℃) until the spasm disappeared.

Observation of vascular diameter changes. Basilar arterial spasm was produced by topical application of a lysed erythrocyte solution. Heparinized whole blood was centrifuged at 2000 g for 15 min, and the supernatant was removed. The packed erythrocyte layer was resuspended in an equivalent volume of saline. Lysis was performed by freezing at −80 ℃ over 12 h and quick-thawing in a 37 ℃ water bath (18). Intravenous administrations of PGI_2 (2 μg/kgBW or 15 μg/kgBW) or papaverine hydrochloride (1.5 mg/kgBW) were made to both normal and erythrocyte-constricted basilar arteries. On the day of usage, PGI_2 methylester was dissolved in 99.5 % ethanol to a concentration of 1 mg/1 ml and diluted in veronal buffer as required. Papaverine was diluted in saline. Two ml of each solution was infused into the cats over one or two min. The arteries were inspected directly through an operative microscope, and serial photographs of the vessels were taken at 2.5 × magnification. Color slides were projected onto a screen, and the inner diameter of the basilar artery was measured at three points. The average vessel diameter and its changes were calculated. When not under observation, the basilar artery was kept in physiological saline (or lysed erythrocyte solution) to maintain a constant diameter. In some cats, the effects of PGI_2 at two different concentrations (2 μg/kg, 15 μg/kg) and papaverine hydrochloride were studied serially. After the lower dose of PGI_2 was assayed, 15 μg/kg PGI_2 was tested. Papaverine hydrochloride was studied last. After each infusion, vessel diameter was observed until the vessel diameter returned to the baseline value.

Observation of regional cerebral blood flow (rCBF) changes. rCBF alteration in the brain

stem (pontine region) was measured in 18 control cats and in 32 cats with SAH. Experimental SAH was produced by injection of 3 to 4 ml of fresh autologous arterial blood into the cisterna magna after removal of an equivalent volume of CSF. The CSF was mixed with two volumes of fresh arterial blood ; this mixture was incubated at 37 ℃ for 3 days. The basilar artery and a part of the brain stem was exposed in the same manner as above, three days after the intracisternal injection of blood. After intravenous administration of various doses of PGI_2 and papaverine hydrochloride, the brain stem rCBF was measured by the heat clearance method (SHINCORDER CTE-202, Japan) using a double needle type element (thermister probe WN-151, MT Giken, Japan). The thermister probe was inserted 5 mm into the brain stem. Prolonged spasm was produced by topical application of the blood-CSF mixture. CO_2 (8 %) in air was also given to all cats and the responses were recorded. 15-HPETE (15-hydroperoxy-5, 8, 11 , 13-eicosatetraenoic acid), dissolved in acetone (1 mg/1 ml) and stored at −80 ℃, was diluted in phosphate buffer. The 2 ml of papaverine (1.5 mg/kgBW) was infused into the cats as above.

RESULTS

Effects of PGI_2 and Papaverine Hydrochloride on the Diameter of the Basilar Artery

The original diameter of the untreated basilar artery exposed transclivally in 21 cats was defined as 100 %. The original MABP averaged 150 mmHg. An injection of 2 μg/kg PGI_2 was followed by a decrease in MABP within 15 sec. Within 90 sec, MABP dropped from 35 to 45 mmHg, and gradually returned to the baseline level in six to nine min in most cats. PGI_2 produced no change in

TABLE 1. RESPONSE OF NORMAL BASILAR ARTERY TO INTRAVENOUS ADMINISTRATION OF PGI_2 OR PAPAVERINE HYDROCHLORIDE

Cat	Percent diameter to the control after admimistration	
	PGI_2 (2 μg/kg)	Papaverive (1.5 mg/kg)
No. 1	93 %	
No. 2	101	
No. 3	103	
No. 4	101	
No. 5	102	137 %
No. 6	98	155
No. 7		132
No. 8		156
No. 9		148
Average	99.7 ± 3.4 %	145.6 ± 9.6 %
p<	Not significant	0.005

The baseline diameter of the normal basilar artery was regarded as 100 % and percent vessel diameter after intravenous administration of PGI_2 or papaverine was calculated.

the diameter of normal basilar arteries in spite of moderate hypotension. The vessel diameter 12 min after 2 μg/kg PGI_2 was injected was 99.7 $\pm$ 3.4 % of the baseline value (Table 1). An injection of 1.5 mg/kg papaverine hydrochloride resulted in a similar decrease in MABP within 20 sec. MABP reached a nadir ranging from 30 to 40 mmHg within one min, and gradually returned to the control level in 2 to 3 min. The basilar arteries began to dilate within 30 sec and showed a maximum dilation, 145.6 $\pm$ 9.6 % of the baseline, 2 min after the infusion (Table 1).

TABLE 2. RESPONSE OF BASILAR ARTERY CONSTRICTED BY A LYSED ERYTHROCYTE SOLUTION TO INTRAVENOUS ADMINISTRATION OF PGI_2 OR PAPAVERINE HYDROCHLORIDE

Cat	Percent diameter after administration			
	Lysed erythrocyte	PGI_2 (2 μg/kg)	PGI_2 (15 μg/kg)	Papaverine (1.5 mg/kg)
No. 1	70 %	70 %	70 %	110 %
No. 2	75.3	92.3	89.6	132.8
No. 3	67.7			119.2
No. 4	68.8	70.3	78.0	
No. 5	64.3	75.7	79.0	125.9
No. 6	54.1			62.2
No. 7	75.8			103.0
No. 8	60.1	66.5	88.6	122.4
No. 9	65.5	66.2		
No. 10	62.2		65.5	
No. 11	76.1		83.3	
No. 12	80.4	76.9	82.5	
Average	68.4 $\pm$ 7.3 %	74.0 $\pm$ 8.4 %	79.6 $\pm$ 7.9 %	110.8 $\pm$ 23.6 %
p<	0.005*	0.005*	0.005*	Not significant*
		Not significant**	0.025**	0.005**

* Against control. ** As compared to the lysed erythrocyte solution. The baseline diameter of the normal basilar artery was regarded as 100 % and percent vessel diameter after treatment was calculated.

The effects of PGI_2 and papaverine on an erythrocyte-induced spasm of the basilar artery were examined. The average diameter of the vessel 30 min after the topical application of the lysed erythrocyte solution was 68.4 $\pm$ 7.3 % (n=12) (Table 2). Intravenous PGI_2 (2 μg/kg) produced a similar change in MABP as in the control cats. The constricted basilar artery began to dilate within 3 to 5 min and demonstrated maximum dilation from 8.5 to 20 min, returning to the baseline within 48 min.

When a higher dose of PGI_2 (15 μg/kg) was infused, MABP began to decrease within 15 sec after the start of the injection. The nadir, which ranged from 65

to 85 mmHg was attained within 2 min and then the MABP returned to the baseline level within 13 to 16 min of the injection. The constricted basilar artery began to dilate between 2.5 min and 6 min, reached maximum dilation in 8.5 min to 18 min and returned to the original diameter in 27 to 40 min. The change in diameter did not parallel that of MABP, with dilation lagging behind the hypotensive effect. Most cats demonstrated maximum dilation of the vessel about 12 min after the injection, regardless of dose. Therefore, the vessel diameter was measured 12 min after the administration. Intravenous administration of either 2 μg/kg or 15 μg/kg PGI_2 resulted in mild dilation of the vessels, with an average of 74.0 ± 8.4 % (n=7) and 79.6 ± 7.9 % (n=8), respectively (Table 2). Branches

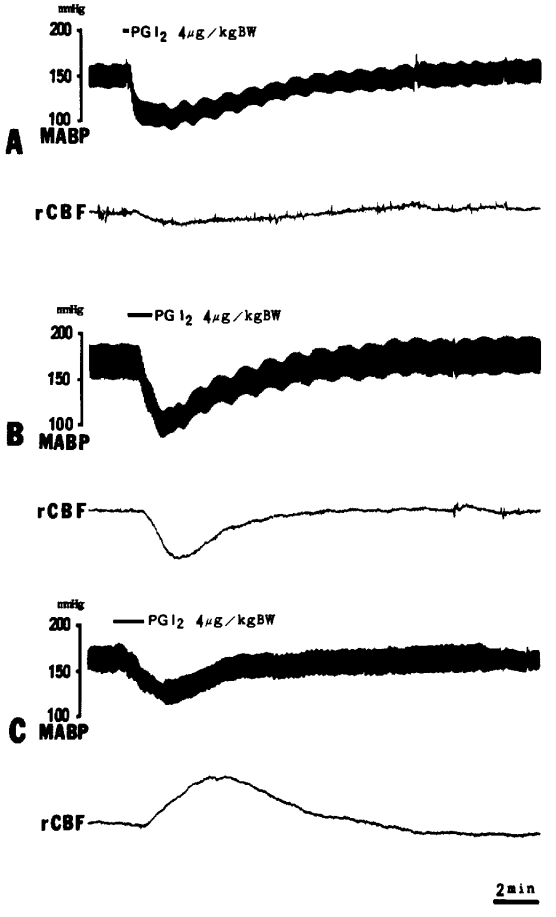

Fig. 1. Change in rCBF after intravenous administration of PGI_2 in normal cats. The patterns of rCBF were of 3 types : Type A (4 cats), no rCBF change : Type B (8 cats), variation of rCBF in relation to MABP, and Type C (1 cat), a transient increase in rCBF despite hypotension. rCBF: regional cerebral blood flow, MABP : mean arterial blood pressure.

of the basilar artery exhibited earlier and more pronounced vasodilation than the main trunk. On the other hand, papaverine hydrochloride (1.5 mg/kg) elicited a diffuse and marked dilation of the constricted vessels and a maximum dilation 2 min after its administration. The average maximum diameter of the vessels was 110.8 ± 23.6 % (n=7) (Table 2).

Effects of PGI_2 and Papaverine Hydrochloride on rCBF in the Brain Stem

Changes in rCBF after intravenous administration of PGI_2

A) *Control group. (13 cats).* Intravenous administration of a small dose (0.05 μg/kg) of PGI_2 elicited no change in MABP. PGI_2 doses of 2 μg/kg and 15 μg/kg decreased MABP to 35 to 45 mmHg and 65 to 85 mmHg, respectively. The

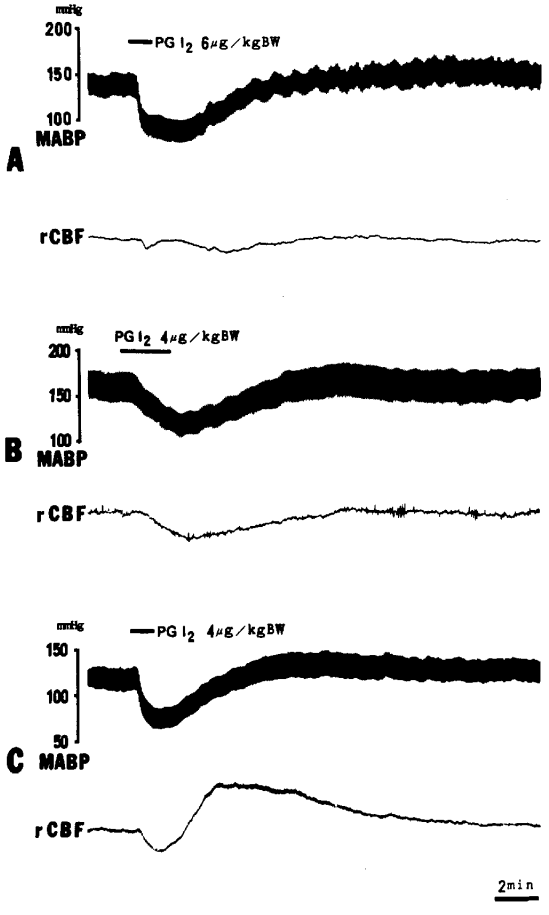

Fig. 2. Change in rCBF after intravenous administration of PGI_2 in cats with experimentally-induced SAH. rCBF patterns were of the same 3 types as in Fig. 1. Type A (11 cats), no change in rCBF. Type B (6 cats), alterations related to MABP. Type C (2 cats) transient increases in rCBF.

nadir was reached within 1.5 min, and the recovery to the baseline was reached in 6 to 9 min, at the lower dose (2 μg/kg). The higher dosage (15 μg/kg) resulted in a maximal depression of MABP at 2 min and recovery in 13 to 16 min. If the depression of MABP was less than 20 mmHg, rCBF did not change. MABP depressions ranging from 20 to 35 mmHg were paralleled by slight alterations in rCBF. MABP decreases greater than 35 mmHg were accompanied by rCBF changes of 3 types (Fig. 1) : Type A (4 cats), no rCBF changes in spite of systemic hypotension ; Type B (8 cats), rCBF changes related to changes in MABP, and Type C (1 cat), an increase in rCBF despite systemic hypotension. When rCBF decreased, as in Type B, the rCBF response lagged approximately 30 sec behind the changes in MABP. In Type C cats, rCBF began to increase within 90 sec

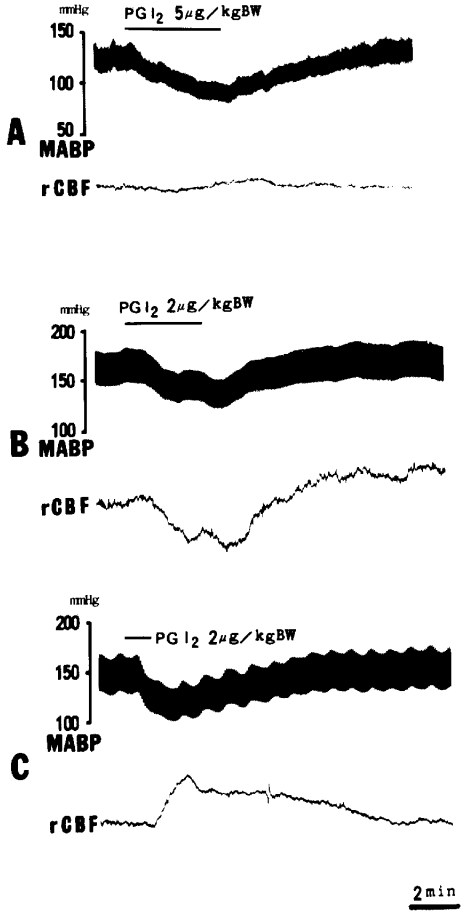

Fig. 3. Effect of PGI_2 on rCBF in cats with experimental SAH administered continuously with 15-hydroperoxy-5, 8, 11, 13-eicosatetraenoic acid (15-HPETE). Changes in rCBF were divided into 3 types as in previous figures. Type A (3 cats), Type B (4 cats) and Type C (1 cat).

of the start of the infusion and returned to the baseline simultaneously with MABP recovery. Various doses of PGI_2 (2, 4, 6 or 15 μg/kg) infused over 30 min resulted in similar types of changes in rCBF. In 13 control cats which received PGI_2 intravenously, either Type A or B was observed in 12 cats, and Type C was observed in only one.

B) *Experimentally-induced SAH group (27 cats).* The effect of an intravenous administration of PGI_2 on rCBF was studied in 27 cats with experimentally induced SAH. Changes in MABP and rCBF were similar to those in the control group. If MABP did not change, either did rCBF. A fall in MABP of over 35 mmHg elicited the same 3 types of changes in rCBF as in the control cats (Fig. 2). A Type A response was seen in 11 cats, Type B in 6 cats and Type C in only 2 cats. Different doses of PGI_2 resulted in the same types of rCBF changes. In one of

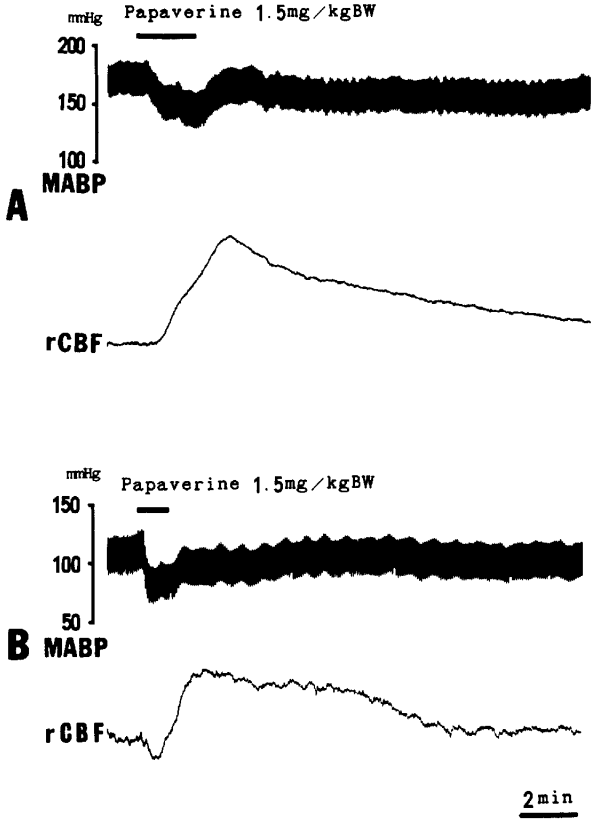

Fig. 4. Effect of papaverine hydrochloride (1.5 mg/kg) on rCBF in untreated cats. The changes in rCBF were of 2 types. Type A (2 cats), a continuous increase in rCBF sustained over 30 min without an initial transient decrease, and Type B (3 cats), a transient increase in rCBF after a transient decrease.

the cats with a Type C response, rCBF decreased transiently in parallel with the decrease in MABP, but it increased above the baseline as MABP recovered. The rCBF pattern in the other cats was similar to that observed in Type C in the control group, that is, a transient rCBF increase.

15-HPETE, which inhibits the synthesis of PGI_2 (2, 19), was diluted in 25 ml of phosphate buffer (pH7.2), and dripinfused into the femoral vein (6 μg/kg/min) of 8 cats. MABP and rCBF responses were similar to those in the other cats (Fig. 3). Type A occurred in 3 cats, Type B in 4 cats and Type C in 1 cat.

All cats, with or without SAH, demonstrated a transient increase in rCBF after the inhalation of 8 % CO_2.

rCBF changes after administration of papaverine hydrochloride

A) *Control group (5 cats).* MABP decreased from 30 mmHg to 40 mmHg with the administration of 1.5 mg/kg papaverine. The fall in MABP began within 30 sec and reached the lowest level in one minute, and returned to the baseline level 2 to 3 min after the initiation of the injection. rCBF varied in the same manner. All cats demonstrated an increase in rCBF. Two cats presented an increase in rCBF, without an initial transient decrease, followed by a continuous increase over 30 min. In the other 3 cats, rCBF began to decrease in 30 sec, then increased over the baseline in one min and finally returned to the baseline level 11 min after the start of the administration (Fig. 4).

B) *SAH group (5 cats).* After administration of papaverine (1.5 mg/kg), the degree of the decrease in MABP and the changes in rCBF were similar to those in the control group. All cats demonstrated an increase in rCBF with (3 cats) or without (2 cats) an initial transient decrease. All cats, regardless of SAH, showed a transient increase after the inhalation of 8 % CO_2.

DISCUSSION

Extensive endothelial cell damage of cerebral vessels has been noted after vasospasm in experimental models (14, 15), as well as in humans who experienced vasospasm (20). It has been suggested that cerebral vasospasm may be secondary to decreased PGI_2 synthesis due to endothelial cell damage (16). A progressive decrease in PGI_2 synthesis observed in the canine basilar artery after experimental SAH has caused speculation that PGI_2 levels may be related to the development of cerebral vasospasm (13). The present study was undertaken to clarify this point and to assess the potential of PGI_2 as a therapeutic agent for cerebral vasospasm. Papaverine not only dilated the cerebral vessel but also increased rCBF in all cats of the present experiments, regardless of SAH, and despite transient hypotension. Papaverine has been shown to be a nonspecific vasodilator of large cerebral and peripheral arteries *in vitro* (21). However, papaverine has not been used clinically in recent years, because of the transient response time, large dosage requirements, and MABP decreases which limit its effectiveness.

Pronounced dilation of the major intracranial vessels has been produced by

venous infusion of PGI_2 in normal baboons (17). This suggests that PGI_2 is of clinical use in the treatment of cerebral vasospasm. Toda (8) has shown that PGI_2 produces only slight or no relaxation of isolated cerebral arteries under basal tone *in vitro*. Some studies have reported that PGI_2 ($1 \times 10^{-8} - 1 \times 10^{-6}$M) dilated isolated arteries contracted by spasmogenic substances (8, 9). Though PGI_2 does not dilate stripped arteries, it is expected that spasmed arteries may respond to PGI_2. In the present study using cats with normal basilar arteries, PGI_2 did not dilate the arteries in spite of moderate hypotension. When PGI_2 ($2\ \mu g/kg = 5.7 \times 10^{-9}$M/kg) is injected intravenously, the systemic circulation dilutes it to a serum concentration of less than 1×10^{-10}M/kg. Thus, blood levels of PGI_2 may not be sufficient. PGI_2 produces dose-dependent systemic hypotension, but its action on the normal large cerebral vessel exhibiting inherent tone seems to be very weak.

It has been reported that PGI_2 causes a dose dependent relaxation of arteries contracted with prostaglandin $F_2\alpha$ ($PGF_2\alpha$) or serotonin (8, 9). In the present study, PGI_2 elicited only slight relaxation of the basilar artery contracted by lysed erythrocytes. Moreover, the change in the constricted artery diameter was not related to the level of MABP. There was a latency period before PGI_2 acted upon constricted arteries, and the degree of dilation was mild. If PGI_2 is a potent vasodilator of cerebral arteries, it should dilate constricted ones shortly after administration as does papaverine. The results suggest that the vasodilatory action site of PGI_2 is in the extracranial arteries as has been noted (8). The branches of the basilar artery were seen to respond earlier and more intensely than the main trunk. This concurs with findings that implicate PGI_2 as acting upon arterioles both peripherally and in the cerebral circulation (6, 10, 11). Therefore, it is concluded that PGI_2 has vasodilating action on cerebral vessels ; and that its main action is on arterioles.

If a PGI_2 deficiency precipitates cerebral vasospasm, administration of PGI_2 should reverse the spasm, and thus increase rCBF. However, rCBF patterns in normal and experimental SAH cats demonstrated no significant differences. Moreover, rCBF increased in only two out of 19 cats with experimental SAH and, the increase was transient. 15-HPETE, which inhibits PGI_2 synthetase (2, 19), was administered in cats with experimental SAH to eliminate endogenous PGI_2. A PGI_2 deficiency should be induced by 15-HPETE, and the administration of PGI_2 should have increased rCBF more significantly in the cats with SAH than the control cats. However, even under these conditions rCBF did not increase in most cats. The diminished PGI_2 synthesis in the arterial wall may not be related causally to cerebral vasospasm, and may be the result of endothelial damage due to the prolonged contraction of the artery following SAH. Although PGI_2 may not reverse cerebral artery spasm, the ability to inhibit platelet aggregation and to dilate arterioles may be useful in adjuvant treatment for cerebral vasospasm.

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