Effects of prostaglandin E₁ on experimental cerebral vasospasm

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This study reports the effects of intraarterial prostaglandin E₁ (PGE₁) upon intracerebral blood flow under control and vasospastic conditions. A new transorbital means of producing acute experimental subarachnoid hemorrhage with concomitant arterial spasm is presented. Two groups of animals were delineated in this investigation. Five animals (Group 1) were extremely sensitive to PGE₁ and subarachnoid hemorrhage (SAH); carotid flow studies with simultaneous intracerebral angiography in this group demonstrated the ability of PGE₁ to relieve vasospasm. Two other animals (Group 2) were relatively insensitive to SAH and PGE₁. The study suggests an important role for PGE₁ in the treatment of intracerebral vasospasm.

KEY WORDS: prostaglandin E₁, subarachnoid hemorrhage, transorbital injection, vasospasm, cerebral blood flow

INTRACRANIAL arterial spasm in patients with subarachnoid hemorrhage (SAH) is associated with a significant degree of morbidity and mortality. There is marked reduction in cerebral blood flow secondary to the development of spasm, and this decrease in flow may result in cerebral ischemia and infarction leading to permanent disability and/or death. The clinical significance of cerebral arterial spasm is further emphasized by the fact that it also occurs in association with craniocerebral trauma.

Although many theories have been suggested to explain intracranial arterial spasm, the topic remains obscure, and treatment unsatisfactory. Various drugs have been used both topically and parentally, in unsuccessful attempts to alleviate spasm. This paper reports the effects of minute amounts of prostaglandin E₁, a safe and potent vasodilator, upon intracerebral arterial spasm, produced by experimental subarachnoid hemorrhage in baboons.

Methods

Seven baboons, weighing between 18 and 24 kg, were selected for this study because of the similarity of the baboon cerebral vasculature to that of man. The animals were sedated with Sernylan (phencyclidine hydrochloride) 7 mg/kg, and maintained lightly anesthetized with intravenous sodium pentobarbital (20 to 60 mg as necessary injected via a polyethylene catheter in a femoral vein). Endotracheal intubation was performed, and the animals were allowed to breathe spontaneously.

Systemic arterial pressure was measured via a catheter in one femoral artery using a transducer, preamplifier, and polygraphic recorder. Through this same catheter all
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Quots of arterial blood were drawn for measurements of pH and blood gases ($pCO_2$, $pO_2$, $O_2$ saturation).†

Central venous pressure was determined through a PE 205 catheter placed directly into an internal jugular vein; the external end of the catheter was attached to a transducer, ‡ and then connected to the recorder.

Bilateral common carotid flow determinations were made using precalibrated 2.5 to 3.5 mm electromagnetic blood flow transducers (Micron). These transducers were placed directly around the proximal portion of the common carotid arteries in the neck. The transducers were then attached to blood flow amplifiers.§ and the recorder. In this manner simultaneous bilateral carotid flow determinations could be constantly monitored. Since the external carotid artery was ligated and used to infuse opaque contrast media or drug, the flowmeter measured internal carotid blood flow. The ECG was also recorded.

Resistance in the carotid circulation was calculated using the following formula: resistance = (mean systemic arterial-central venous pressure) divided by cerebral blood flow expressed as mm Hg/mL/min.

It has been previously noted that arterial spasm can best be obtained through injection of fresh autogenous whole blood into the chiasmatic cistern. 22 The techniques of Lougheed and Tom, 11 and McQueen and Jeanes 22 were found adequate but cumbersome and time-consuming for an "acute" experiment. The following modification was therefore developed and used: a 3½ in. disposable spinal needle was inserted transorbitally through the extreme lateral aspect of the right orbit, piercing the globe and continuing through the optic foramen (Fig. 1). The dura was pierced in a manner similar to that of a lumbar puncture. The stylet was then withdrawn and the needle advanced cautiously. Clear cerebrospinal fluid from the chiasmatic cistern appeared almost immediately; 2 mL of air were instilled and needle placement in the chiasmatic cistern verified by a lateral skull film. "Subarachnoid hemorrhage" was then easily simulated by the injection of 5 mL of whole autogenous blood at a rate of 1 mL/15 sec through the spinal needle into the chiasmatic cistern. In five of seven animals angiographic evidence of severe spasm of the vessels of the circle of Willis was obtained within 20 min.

A PE No. 90 catheter was inserted in a retrograde manner in the right external carotid artery. This artery was ligated distally. The tip of the catheter remained at least 1 cm above the carotid bifurcation in the external carotid artery. Then 6 mL of meglumine iothalamate (Conray 60) were injected through this polyethylene catheter. Single lateral radiographs were taken using a Picker portable x-ray unit fitted with a mastoid cone; a technique of 200 mA, 62 kV, and $\frac{1}{3}$ sec exposure time was utilized. A fixed distance was maintained between the x-ray cone, the animal's head, and the x-ray film, to insure consistency in magnification.

Initial control values of bilateral carotid flow were determined and simultaneous angiography performed. Prostaglandin $E_1$ (PGE$_1$) in doses ranging from 1 to 100 ng/kg/min was administered through the polyethylene catheter in the right external carotid

Fig. 1. Transorbital approach to the chiasmatic cistern. Note the lateral placement of the spinal needle piercing the globe.

† Radiometer, Astrup.
‡ Statham Transducer model P2388.
§ Biotronix, model 310.
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**TABLE 1**

*Summary of results*

<table>
<thead>
<tr>
<th>Group</th>
<th>Right Common Carotid</th>
<th>Left Common Carotid</th>
<th>Mean Blood Pressure (mm Hg)</th>
<th>Angiographic Degree of Arterial Spasm</th>
<th>Deaths</th>
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<tr>
<td></td>
<td>Flow (mL/min)</td>
<td>Mean Resistance (R)</td>
<td>Flow (mL/min)</td>
<td>Mean Resistance (R)</td>
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<tr>
<td><strong>Group 1 (5 baboons)</strong></td>
<td></td>
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<tr>
<td>Control</td>
<td>85±9</td>
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<td>1.41</td>
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<td>60±7</td>
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<td>marked</td>
</tr>
<tr>
<td>PGE1</td>
<td>64±5</td>
<td>1.62</td>
<td>82±7</td>
<td>1.46</td>
<td>104 marked</td>
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<td>10 ng/kg/min</td>
<td>72±6</td>
<td>1.33</td>
<td>82±7</td>
<td>1.46</td>
<td>104 moderate</td>
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<tr>
<td>100 ng/kg/min</td>
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<td>1.42</td>
<td>104 minimal</td>
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<td>Control</td>
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| artery. (Note: 1 ng (nanogram) = 1 billionth of a gram or 10^-9 gm.) Bilateral carotid flow values were monitored continuously. Cerebral angiography was repeated when carotid flow on the side of PGE1 administration was double that of the control value. Each dose of PGE1 was administered with the use of the Harvard constant infusion pump. Twenty minutes were allotted as the interval of time each successive dose of PGE1 was to be used. After the last dose, animals returned to control conditions usually within 3 to 5 min.

Experimental SAH was then induced by the method previously described. Angiography was repeated in 20 min to document spasm of the vessels of the circle of Willis. PGE1 was then administered in successive doses of 1, 10, 100, and 200 ng/kg/min, and was followed by intracerebral angiography again at 20-min intervals. Carotid flow values were correlated with the angiographic findings to document the effect of PGE1 on intracerebral vasospasm.

The brain of each experimental animal was examined immediately after completion of the experiment to verify the presence of SAH. The brains were fixed in 10% formalin solution and coronal sections made 7 days later.

**Results**

Two groups of baboons were delineated (Table 1). Group 1 contained five baboons.
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whose cerebral vessels were exquisitely sensitive to both SAH and intraarterial PGE₁ while the two animals in Group 2 were relatively insensitive (Fig. 2).

**Group 1**

Small initial doses of PGE₁ (1 to 10 ng/kg/min) increased control carotid flow values and decreased resistance bilaterally. On the side of administration of the PGE₁, carotid flow was doubled within 2 min. Intracerebral angiography performed while control carotid flow was increased did not reveal significant vasodilatation when compared with control angiograms. When perfusion of PGE₁ was halted, blood flow returned to control values within 3 to 5 min.

Following instillation of 5 mL of blood in the chiasmatic cistern, the Group 1 animals responded dramatically; all the baboons showed transient episodes of apnea, arrhythmias, bradycardia, and systemic arterial hypotension; two exhibited generalized seizures followed by progressive deterioration and death. The surviving baboons showed a marked bilateral decrease in carotid flow noted almost simultaneously with the instillation of blood into the chiasmatic cistern. Carotid flow decreased an average of 50% on the same side as the injection of blood into the subarachnoid space. Angiography revealed moderate to marked spasm within 20 min of the SAH. This spasm involved major arteries of the circle of Willis as well as the extradural segment of the internal carotid artery (Fig. 3).

Carotid flow was increased and the spasm alleviated by the intraarterial infusion of PGE₁. Following SAH, much larger doses (100 to 200 ng/kg/min) were necessary to increase carotid flow twofold, as compared with the small doses (1 to 10 ng/kg/min) able to produce comparable effects under control conditions (Fig. 2). Intracerebral angiography revealed significant release of vasospasm only at these higher doses of PGE₁ (Fig. 3). Upon discontinuation of PGE₁ infusion, carotid flow decreased bilaterally, and repeat angiography revealed return of the spasm.

**Group 2**

There were two baboons which were relatively insensitive to SAH and PGE₁ (Table 1). In these animals SAH produced little, if any, clinical signs and little change in carotid flow or resistance while only a large dose (100 ng/kg/min) of PGE₁ would increase control carotid flow values significantly on the side of administration. Even with increased subarachnoid hemorrhage (10 mL), spasm could not be demonstrated angiographically or by a decrease in carotid flow.

In both Groups 1 and 2, SAH was documented in all the animals by postmortem examination; in each case the hemorrhage was diffuse and marked. It was also noted that throughout the experiments intraarterial PGE₁ had no observable effects on systemic blood pressure, respiration or the electrocardiogram (ECG).

**Discussion**

In 1935 von Euler² described a lipid found in human seminal plasma which had smooth-muscle-stimulating properties. This lipid was termed prostaglandin because the discoverer felt that it originated from the prostate gland. In 1962 the chemical structure of prostaglandin was delineated,² and 2
years later it was determined that this "hormone" is synthesized in the body from essential fatty acid precursors. At present four major series of prostaglandins are recognized, namely prostaglandins E, F, A, and B. All four series are chemical derivatives of prostanoic acid, and each series varies in specific biological function. The prostaglandins are believed to be present in almost all organ systems, and may be an "invariable constituent of all cells."

Prostaglandin E₁ was selected for this investigation for two major reasons. It is a naturally occurring substance in man and therefore an agent with less risk of untoward side effects, and it is an extremely potent vasodilator in other peripheral circulations, effective in doses of nanograms. At present the exact mechanism by which PGE₁ produces vasodilation has not been delineated. It has been proposed that PGE₁ may act directly on smooth muscle, and/or alter the active transfer of calcium ions across interfaces, resulting in vasodilation.

In our study, the cerebral circulation, which is often considered rather insensitive to vasodilators because of its autoregulatory capacities, was highly reactive to PGE₁. In fact, internal carotid flow increased to a greater extent than mesenteric arterial flow with similar doses of PGE₁.

After SAH in sensitive (Group 1) baboons, a reflex fall in carotid flow occurred to levels 50% below control values. Clinically this may represent a protective mechanism by which flow is decreased to the parent artery feeding an injured circulation, e.g., a ruptured aneurysm. This can be occasionally demonstrated angiographically in man by noting extension of spasm into the extradural segments of the internal carotid artery. It was interesting to note that in animals relatively insensitive to PGE₁ (Group 2) no significant fall in carotid flow occurred with SAH, and cerebral vasospasm could not be demonstrated by angiography. We have no explanation for the variation in response of the two groups of animals.

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Fig. 3. Baboon 4. Left: Lateral right carotid arteriogram made 20 min after experimentally induced SAH. Note the severe spasm of the internal carotid artery (I.C.A.) with almost no flow to its branches and shunting of contrast medium to the posterior neck region. Right: Following PGE₁ infusion, flow is reestablished in the internal carotid system.

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Summary

The effects of prostaglandin E\textsubscript{1}, a potential spasmolytic agent, were studied in seven baboons before and after experimentally induced subarachnoid hemorrhage. In five animals (Group 1) control carotid flow values were increased twofold when minute amounts of prostaglandin were administered intraarterially. Of these five animals, two died and three survived with marked intracerebral vasospasm following subarachnoid hemorrhage. The vasospasm was documented by intracerebral arteriography, a decrease in internal carotid blood flow, and an increase in vascular resistance in the carotid circulation. In these animals, prostaglandin E\textsubscript{1} when reinjected relieved spasm, increased carotid flow bilaterally, and decreased resistance.

In two animals (Group 2), control values of carotid flow could be increased 50% but with a somewhat larger dose of the drug (100 ng/kg/min). These animals appeared not only relatively insensitive to prostaglandin E\textsubscript{1} but also to subarachnoid hemorrhage.

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