Effect of Intracarotid Prostaglandin E₁, on Regional Cerebral Blood Flow in Man

JES OLESEN, M.D.

SUMMARY The effect of prostaglandin E₁, on regional cerebral blood flow (rCBF) was studied with the intra-arterial ¹³³Xe method in ten awake patients under local anesthesia. Measurements were taken from 16 areas of a hemisphere in seven patients, from 35 areas of a hemisphere in two patients and from 256 areas of a hemisphere in one patient. The prostaglandin was dissolved from the crystalline state without the aid of alcohol. It was given intracarotidly as a constant infusion at a rate of 5 ng per kilogram per minute for five minutes before the measurement, and continued during the measurement. In every patient a mild increase in blood flow during the prostaglandin infusion was seen. The flow increase took place in all parts of the hemisphere. It averaged 11.2% (p < 0.01). During the infusion, the skin supplied by the internal carotid artery and the conjunctiva on the infused side became red and sometimes swollen. A slight pressure was noted by most patients, but none had pain. No side effects of the infusion were noted.

THE PROSTAGLANDINS are a large family of naturally occurring substances with a variety of biological actions. In a number of organs they are vasoactive. Prostaglandin E₁, is known to markedly increase blood flow to human skin and muscle.¹

The effect of prostaglandin E₁, on cerebral blood flow (CBF) and pial vessel diameter has been studied previously in animals. Published results, however, have been contradictory.² ³ There is rapidly growing interest in the widespread and important physiological actions of prostaglandins. Recently, it has been suggested that prostaglandins liberated from the lungs may play a part in the pathogenesis of migraine attacks.⁴ To possibly resolve the above-mentioned discrepancies and to gain knowledge of the prostaglandin action in humans, it was decided to study the effect of con-

References

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**TABLE 1** PGE, and rCBF: Clinical Material

<table>
<thead>
<tr>
<th>Pt. no./age/sex</th>
<th>Case history</th>
<th>Angiographical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/51/F</td>
<td>During 3 months several L-sided focal epileptic attacks. On examination spastic L-sided hemiparesis. Operation showed a small subcortical glioblastoma in the premotor region.</td>
<td>Normal</td>
</tr>
<tr>
<td>2/33/M</td>
<td>During 6 months increasingly slow and unsteady gait. On examination paratonia and L optic atrophy.</td>
<td>Partial callosal agenesis</td>
</tr>
<tr>
<td>3/62/F</td>
<td>During 1 year progressing dementia and urinary incontinence. Neurological examination normal except for dementia. A large Falx meningioma was removed at operation.</td>
<td>Large R-sided frontal mass</td>
</tr>
<tr>
<td>5/48/F</td>
<td>From October, 1974, gradually progressing L hemiparesis, vertigo and headache.</td>
<td>Large mass centrally in L hemisphere</td>
</tr>
<tr>
<td>6/71/M</td>
<td>During the last 2 years several admissions for arteriosclerotic heart disease. Admitted after R-sided focal epileptic attack with persistent mild R hemiparesis.</td>
<td>Normal</td>
</tr>
<tr>
<td>7/71/M</td>
<td>During 4 years gradual development of dementia. Admitted after fainting spell. Mild L hyperreflexia.</td>
<td>Normal</td>
</tr>
<tr>
<td>8/62/F</td>
<td>1963: sudden onset of L hemiparesis, probably CVA. Since then grand mal epilepsy with postictal L hemiparesis. At the time of study only minimal hemiparesis.</td>
<td>Slight arteriosclerosis</td>
</tr>
<tr>
<td>9/64/M</td>
<td>Anaplastic tumor in L thigh, probably reticulosarcoma. Admitted after gradually increasing mental deterioration, vertigo, fatigue and clumsiness of L hand. On examination, mild L hemiparesis.</td>
<td>Tumor deeply situated in R hemisphere</td>
</tr>
<tr>
<td>10/71/F</td>
<td>During 1 year complaints of burning and pain in the tongue. On examination markedly demented without focal deficits.</td>
<td>Normal</td>
</tr>
</tbody>
</table>

During the infusion of prostaglandin a marked reddening and sometimes swelling of the skin of the glabellar region on the infused side was noted. The conjunctiva on the infused side became red and swollen (fig. 1). The patients experienced a feeling of pressure around the eye, but there was no definite pain or discomfort. No patient complained of alcohol. It was supplied in a solution of 50 micrograms per milliliter and was kept frozen. After thawing the solutions were not used again for the purpose of this study.

**Results**

During the infusion of prostaglandin a marked reddening and sometimes swelling of the skin of the glabellar region on the infused side was noted. The conjunctiva on the infused side became red and swollen (fig. 1). The patients experienced a feeling of pressure around the eye, but there was no definite pain or discomfort. No patient complained of

![Figure 1. Left: the territory of facial skin supplied by the internal carotid artery is demonstrated during injection of Evan's blue. Right: the same patient during infusion of 5.0 ng PGE, per kilogram per minute. During infusion, the skin was markedly red and the conjunctiva on the infused side was injected. In some patients edema of both skin and conjunctiva could be seen.](http://stroke.ahajournals.org/)

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**Figure 1.** Left: the territory of facial skin supplied by the internal carotid artery is demonstrated during injection of Evan's blue. Right: the same patient during infusion of 5.0 ng PGE, per kilogram per minute. During infusion, the skin was markedly red and the conjunctiva on the infused side was injected. In some patients edema of both skin and conjunctiva could be seen.
headache. Speech, motor skills and the level of consciousness were unaffected.

All significant results of the investigation are listed in Table 2. The lower doses of 0.1 and 1.0 ng per kilogram per minute had no obvious effect on CBF. But infusion of 5.0 ng per kilogram per minute resulted in a significant increase in CBF in every patient. The blood flow increase averaged 11.2%, and the effect was significant at the 0.01 level whether or not correction for the very small differences in Paco2 was carried out (Wilcoxon's rank sum).

In all patients rCBF was measured from several regions of the hemisphere. One patient was studied with 256-channel equipment, two patients with 35-channel equipment, and seven patients with 16-channel equipment.

Using visual analysis of the flow response of various regions of the brain to PGEi, no major difference between regions could be demonstrated.

Discussion

The effect of a circulating drug on CBF is dependent on its ability to cross the endothelium of the brain vessels, particularly the arterioles as discussed by Olesen. The literature does not contain specific information concerning the passage of prostaglandin E1 from blood to brain. However, from the chemical structure of the prostaglandins (fatty acids with strongly dissociated carboxy groups), one would expect the passage across the blood-brain barrier to be very slow, unless active transport mechanisms were operating. Studies in which prostaglandins are administered into the CSF, therefore, probably are not directly comparable to studies of the effects of circulating prostaglandins.

With topical application of prostaglandin E1 to pial arterioles, a marked vasoconstrictor effect has been found in the dog. These investigators also found that intracarotid infusion of prostaglandin E1 caused a marked vasoconstriction and decrease in CBF in the dog. If the prostaglandin was dissolved with the aid of alcohol, the constrictor effect on the brain vessels was absent. Contradictory results were found in the baboon. Here prostaglandin E1 infused into the common carotid artery through the tied-off external carotid artery relieved cerebral vasospasm induced by subarachnoid blood. Carotid blood flow was clearly increased by prostaglandin in a dose-related manner.

Steiner et al. studied the effect of prostaglandin E1 on CBF and cerebral arterial diameter in patients with subarachnoid hemorrhage and cerebral vasospasm, and found no significant effect on either parameter. The doses were comparable to those in the above-cited animal studies and somewhat higher than those of the present study.

It has been argued that the reason for the discrepancy in previous findings was that most investigators had used small amounts of ethylalcohol to dissolve the prostaglandin E1.

The aim of the present study was to evaluate the effects of prostaglandin E1 on the human cerebral circulation when the agent was dissolved without the use of alcohol and when the brain vessels were not in spasm. The results were uniform, since all ten patients showed a modest increase of rCBF in all regions studied. It should be noted that in our experiment, conditions were as physiological as possible: no anesthesia or premedication was used, and at least some of the patients were neurologically fairly intact.

It can be safely concluded, therefore, that prostaglandin E1 is a vasodilator in the human brain just as in other organs. This is so whether or not it has been dissolved with alcohol. When the effect is modest in comparison to the effect in other organs, it is probably due to the blood-brain barrier, which impedes its passage to the smooth muscle receptor sites.

In every patient the marked vasodilatation in the supraborbital skin and the conjunctiva served as witness of the potency of the infused solution. The area of reddishness roughly corresponds to the area of pain in cluster headache. However, the patients did not have pain. Other vasoactive substances in the internal carotid blood may be responsible for the pain in cluster headache.

None of our patients were migraineurs. Therefore, we cannot eliminate the hypothesis of Sandler that prostaglandins liberated from the lungs may be implicated in the pathogenesis of migraine attacks. None of our patients, however, reacted with hemicrania-like headache during or after the challenge with these physiologically high doses of prostaglandin E1.

### Table 2: Effect of Intracarotid PGE1 on rCBF in Man

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Dose (ng/kg/min)</th>
<th>MAPB (mm Hg)</th>
<th>Paco2 (mm Hg)</th>
<th>Mean hemispheric rCBF (ml/100 gm/min)</th>
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<tr>
<td></td>
<td></td>
<td>Rest</td>
<td>PGE1</td>
<td>Rest</td>
</tr>
<tr>
<td>1</td>
<td>0.1</td>
<td>70</td>
<td>77</td>
<td>48.6</td>
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<tr>
<td>-</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>-</td>
<td>5.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>75</td>
<td>75</td>
<td>45.0</td>
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<td>4.0</td>
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<td>-</td>
<td>-</td>
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<td>3</td>
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<td>29.1</td>
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<td>5</td>
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<td>123</td>
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<td>6</td>
<td>5.0</td>
<td>87</td>
<td>90</td>
<td>47.8</td>
</tr>
<tr>
<td>7</td>
<td>5.0</td>
<td>?</td>
<td>?</td>
<td>34.5</td>
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<tr>
<td>8</td>
<td>5.0</td>
<td>?</td>
<td>?</td>
<td>42.2</td>
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<td>9</td>
<td>5.0</td>
<td>90</td>
<td>93</td>
<td>34.2</td>
</tr>
<tr>
<td>10</td>
<td>5.0</td>
<td>140</td>
<td>140</td>
<td>40.1</td>
</tr>
</tbody>
</table>

*Not included in average values.
Paradoxical Dilatation of the Large Cerebral Arteries in Hypocapnia in Man

E. W. Radó, M.D.,* and G. H. Du Boulay, M.B., F.R.C.P., F.R.C.R.†

SUMMARY By grouping patients who had carotid angiograms under unusually carefully monitored conditions it has been shown that hypocapnia is associated with vasodilatation at low blood pressure but not at high blood pressure. The mechanism is discussed in general terms and it is suggested that the hypocapnic vasodilatation may be a response to cerebral hypoxia and may be transmitted via an intracerebral autonomic pathway. Clinical and angiographical diagnoses are given for 50 patients.

IN THE BABOON there is angiographical evidence that during hypocapnia the response of the larger cerebral arteries to a further drop in Paco₂ is vasodilatation. This paradoxical reactivity was also observed in man, but the conditions under which diagnostic angiography had to be performed in the hospital could not be as carefully controlled as in the experiments with baboons, so that in man the effects of concomitant blood pressures (BP) were unknown.

To investigate the phenomenon further we have measured the internal diameters of the intracranial carotid, the middle and the anterior cerebral arteries in a series of angiograms which were all carried out under unusually carefully monitored conditions. The arterial diameters have been related both to blood pressure and Paco₂. The findings indicated that though paradoxical CO₂ reactivity is generally seen at low blood pressure in hypocapnic patients, it is not seen if a normal blood pressure is maintained.

Methods

From patients at The National Hospital, Queen Square, London (England) who were anesthetized using a short-acting barbiturate for inductions and who were maintained on nitrous oxide and oxygen, supplemented by neuroleptanalgesia in order to carry out intracarotid ¹³³Xe cerebral blood flow (CBF) studies and carotid angiography, 40 were chosen because their blood pressure levels fitted into our predetermined grouping. Ten further patients had had angiography at St. Bartholomew's Hospital also under very carefully monitored conditions, but anesthetized (after induction with a minimal proportion of halothane) with N₂O and O₂ only. Clinical and angiographical diagnoses are given in table 1.

In both groups of patients mean arterial blood pressure and PACO₃ were recorded immediately before the AP angiography series of films. In some of the St. Bartholomew's Hospital patients CO₂ was added to the inspired gases in order to return the PACO₂ to normal levels before a second series of films had to be made, and the opportunity was taken to compare the diameters of the vessels with what they had been before.

From the angiograms thus obtained from 50 patients, six groups were made of ten studies each, depending upon the levels of blood pressure and PACO₂. The grouping was arranged by mean blood pressures, low (75 mm Hg and below), medium (75 to 100 mm Hg) and high (above 100 mm Hg). PACO₂ readings were split into those at and below 28 mm Hg and those of 29 mm Hg or more. Thus, the six groups of studies each were those with: (A) medium BP/high PACO₂, (B) medium BP/low PACO₂, (C) high BP/high PACO₂, (D) high BP/low PACO₂, (E) low BP/high PACO₂, (F) low BP/low PACO₂.

The significance of the differences between the parameters used for grouping is in tables 2 and 3.

Having thus achieved what appear to be significantly different groups around a point at a PACO₂ of 28 mm Hg, it was thought that comparison of mean arterial diameters between groups might show whether the reactivity of these vessels is likely to be the same or different above and below the critical PACO₂ level chosen.

Results

The basic results are set out in table 4. The mean values of the diameters of each of the three arteries were compared

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