Treatment of Acute Focal Cerebral Ischemia with Prostacyclin

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SUMMARY The object of this investigation was to study the effects of prostacyclin (PGI₂) upon the evolution of acute focal cerebral ischemia in the cat. Twenty-five fasted adult cats, lightly anesthetized with nitrous oxide, underwent right middle cerebral artery (MCA) occlusion. Eleven cats received an intracarotid infusion of PGI₂ in buffered saline pH 10.5 (100 ng/kg/min at 0.01 ml/kg/min), and 11 cats received intracarotid buffered saline pH 10.5 (0.01 ml/kg/min) without therapeutic agents. Treatment with PGI₂ was started upon MCA occlusion and continued for 6 hours. Thirty minutes prior to perfusion, the animals were given fluorescein and Evans blue by intravenous injection. The cats were perfused-fixed in vivo with carbon and buffered formalin 6 hours after MCA occlusion. Another 3 cats received tritium labeled intracarotid PGI₂, and peripheral venous samples were collected and assayed for PGI₂ plasma levels. Mean arterial pressure was stable in PGI₂ treated animals during 6 hours of MCA occlusion, while untreated cats had significant progressive hypertension during that period. The rCBF (measured by the intracarotid ¹³³Xe method) decreased markedly in all animals immediately upon MCA occlusion. However, untreated animals had a significant progressive improvement in rCBF during the occlusion period, while PGI₂ treated animals had no such improvement. Quantitative EEG changes, gross edema, areas of fluorescein extravasation, patterns of carbon perfusion, and infarct size were not significantly different in the two groups. While most untreated animals had marked Evans blue extravasation after 6 hours of MCA occlusion, most PGI₂ treated animals had no such extravasation, indicating some protection of the blood-brain barrier in these animals.

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AN EFFECTIVE MEDICAL REGIMEN for the treatment of focal cerebral ischemia has yet to be defined. Therapy ideally should be directed towards improving tissue perfusion, reducing edema, and increasing the tolerance of cerebral tissue, particularly neurons, to the effects of ischemia. ¹ It is unlikely that a single agent will be found to accomplish all these goals. Recent investigations have suggested that progressive microcirculatory impairment² ³ and intravascular coagulopathy⁴ occur in the ischemic brain. Other studies have described increased resistance of pial arteries following experimental middle cerebral artery (MCA) occlusion.⁵ Although it is not known to what extent this microcirculatory impairment contributes to the progression of ischemic changes and neurological damage, it is felt that maintenance of the cerebral microcirculation may enhance the delivery of oxygen and substrate, and potentially allow delivery of other therapeutic agents to the core area of ischemia. Prostacyclin (PGI₂) is a prostaglandin with short half life, synthesized in large quantities in blood vessel walls, including large and small cerebral arteries.⁶ It is a potent vasodilator and inhibitor of platelet aggregation. Another short-lived prostaglandin, Thromboxane A₂ (TXA₂), is synthesized in the platelet itself, and possesses vasoconstricting and platelet aggregating properties. Both compounds exert their effect via the intracellular messenger, c-AMP, with PGI₂ increasing intracellular c-AMP concentration, and TXA₂ decreasing it.⁷ ⁸

Under normal conditions, a balance is thought to exist between the effects of PGI₂ and TXA₂.⁷ ⁸ It has been suggested that this PGI₂-TXA₂ homeostasis may be perturbed in certain pathological states including cerebral vasospasm,⁹ transient ischemic attacks,¹⁰ and the "no-reflow phenomenon" observed after complete generalized ischemia.¹¹

There is, however, no direct evidence that the PGI₂-TXA₂ mechanism plays an important role in focal cerebral ischemia. The objective of this investigation was to study the effect, if any, of PGI₂ upon the evolution of cerebral infarction after right MCA occlusion in the cat.

Methods
Animal Model and MCA Exposure
Anesthesia was induced in 22 fasted adult cats (mean weight 3.9 kg) using ketamine hydrochloride (40 mg/kg intraperitoneally). Administration of ketamine hydrochloride took place at least 2 hours before MCA occlusion and no additional doses were given. Catheters were inserted into the right femoral artery and vein through a groin incision. A tracheostomy was performed and mechanical ventilation instituted. Light anesthesia was maintained throughout the experiment using 75% nitrous oxide, and all animals were paralyzed with d-tubocurarine chloride (0.75 mg/kg/hour) administered in a continuous normal saline infusion (5 ml/kg/hour). Previous experience with this model revealed that such continuous fluid replacement maintains a stable hematocrit throughout the experiment. All animals received in addition, one dose of atropine sulfate (0.6 mg/kg) subcutaneously one hour prior to MCA occlusion to reduce secretions.

Subcutaneous needle electrodes were placed for EKG recording. A 22-gauge catheter was inserted into the right common carotid artery through the lingual artery for subsequent injection of Xenon-133 (¹³³Xe), and for the administration of PGI₂. Arterial blood gases and hematocrit were determined prior to each regional...
cerebral blood flow (rCBF) measurement, and as necessary, to maintain the PaO \(_2\) above 100 mmHg, and the PaCO \(_2\) in the 30–35 mmHg range (i.e., normal range for conscious adult cats). Arterial blood pressure (femoral artery), pulse rate, and EKG were monitored continuously. A heating pad was placed over the trunk to maintain the core temperature at 37°C.

The head of each cat was shaved and placed in a headholder with unobstructed access to the right orbit. Orbital contents were evacuated on the right side, and a small craniectomy performed unroofing the optic foramen. Using microsurgical techniques, a cruciate incision was made in the dura mater. The arachnoid membrane was then slit longitudinally over the right MCA. The proximal MCA was dissected carefully from the adjacent structures in preparation for application of the miniature aneurysm clip.

**Regional Cerebral Blood Flow**

The scalp and temporalis muscles were removed bilaterally from the skull. Regional cerebral blood flow was measured by the \(^{133}\)Xe clearance technique. The \(^{133}\)Xe window (centered at 81 keV) was determined with the multichannel analyzer. A collimated 1.5 cm sodium iodide crystal recessed 5.0 cm was applied to the skull overlying the right Sylvian cortex. Two hundred microCuries of \(^{133}\)Xe in 0.5 ml normal saline was rapidly injected into the right carotid artery through the lingual artery catheter. Radioactivity counts were recorded on a multichannel analyzer for a 10-minute period. The rCBF was calculated from kinetic analysis of the \(^{133}\)Xe washout curve. These measurements were performed immediately before and immediately after MCA occlusion, and at 3 hours and 6 hours post-occlusion.

**Electroencephalography**

Prior to MCA occlusion, small holes were drilled bilaterally 1.0 cm from the midline on the previously exposed skull. The holes were placed in the midfrontal, posterior frontal, and parietal regions bilaterally. Small stainless steel bolt electrodes were screwed into these holes to a depth contacting but not penetrating the dura. The location of the electrodes was in the border zone between the anterior cerebral artery and middle cerebral artery territories and not in the core area of ischemia (i.e., Sylvian region). Another hole was drilled in the midline over the frontal air sinus and the screw was inserted for use as a reference electrode. The left temporal muscle was used for a ground. Tracings were recorded on a Grass model 6 electroencephalograph with recorded amplitudes 20% down at 1 and 70 Hertz. The EEG was recorded throughout the peri-occlusion period, and then for 2 minute periods every hour for the duration of the experiment.

**Treatment Groups**

The animals were alternately assigned to treated and untreated groups (11 animals in each group). The treated cats received 0.01 ml/kg/min of 0.9% saline buffered to pH 10.5 with Na\(_2\)CO\(_3\) and containing 10 \(\mu\)g/ml of PGI\(_2\) (i.e., 100 ng/kg/min) as a continuous infusion through the right carotid artery catheter. Untreated animals received 0.01 ml/kg/min of buffered saline (pH 10.5) without PGI\(_2\). The infusion was started at the time of right MCA occlusion and continued for 6 hours.

Prostacyclin solutions were prepared immediately prior to the experiment from a more concentrated solution (1.0 mg/ml). The infused material was kept on ice throughout the treatment period. The infused solution was periodically assayed for PGI\(_2\) concentrations using high pressure liquid chromatography (HPLC). No significant breakdown of PGI\(_2\) was noted under these conditions.

**Right Middle Cerebral Artery Occlusion**

After the pre-occlusion rCBF determination, the exposed right MCA was occluded with a miniature Mayfield aneurysm clip. The clip was placed as close to the origin of the MCA as possible, proximal to the thalamostriate branches. The clip remained in place for the 6-hour treatment period.

**Perfusion Technique**

Thirty minutes before perfusion, Evans blue and sodium fluorescein (0.5 ml of a 10% solution of each) were given intravenously. Intra-arterial carbon fixative perfusion was carried out at the end of the 6-hour ischemic period. A midline thoracotomy was performed, and a large cannula was passed through a left ventriculostomy into the ascending aorta and secured with a ligature. The descending aorta was clamped and the right atrium incised. The right MCA was reopened immediately prior to perfusion by removing the aneurysm clip in order to improve delivery of the carbon fixative solution to the ischemic tissue. The animals were perfused with 50 ml of isotonic saline followed by a mixture of colloidal carbon (125 ml) and phosphate buffered 4% formaldehyde (125 ml) at a constant pressure of 120 mm Hg. The brain of each cat was removed, sliced coronally, and placed in a fixative solution for 48 hours.

**Examination of the Brain**

The coronal brain slices were photographed. The presence or absence and distribution of fluorescein or Evans blue staining was noted. The shift of the midline structures, if any, was measured. The distribution of carbon staining was graded according to a previously described system. Grade "0" indicated normal carbon filling in cortical and subcortical gray matter. Grade "1" referred to a few circumscribed foci of poor filling not more than 3 mm in diameter. Grade "2" indicated a large area of improper subcortical filling, while Grade "3" referred to an extensive cortical and subcortical region of impaired filling.

Thin (10\(\mu\)m) semi-serial coronal sections were prepared from paraffin-embedded slides of both hemispheres, stained with hematoxylin and eosin and periodic acid Schiff stain, and examined with a light microscope. Ischemic neuronal alterations were grad-
ed blindly by a single investigator according to a previously established classification (Grades I, II, or III). The cross-sectional area of gray matter, where moderate and severe neuronal alterations (i.e., Grade II and III) predominated, was determined with a Keuffel and Esser planimeter (Keuffel and Esser Company, New York, New York) in coronal sections of the right cerebral hemispheres 3 mm posterior to the temporal lobe tip. The percentage of gray matter surface area where moderate and severe ischemic neuronal alterations predominated was determined (ischemic gray area/total gray area × 100).

Sham Control

Six animals underwent the same experimental regimen without occlusion of the right MCA. The dura mater and arachnoid membrane were opened in these animals and the MCA dissected, but no aneurysm clip was placed. Three animals underwent a 6-hour intracarotid infusion of buffered saline, while the other 3 cats received the buffered solution containing PGI₂ in a similar fashion to the untreated and treated groups respectively. Cerebral blood flow was measured at 2-hour intervals throughout the infusion, and the animals were perfused and their brains examined as described above.

Prostacyclin Pharmacokinetics

Three additional animals were subjected to right MCA occlusion and received an intracarotid PGI₂ infusion containing a known fraction of tritium labeled PGI₂. The total PGI₂ concentration in the infused solution and the rate of infusion were identical to those used in the treated animals. Peripheral venous samples were collected at 15-minute intervals and assayed for tritium labeled PGI₂ using a chemical assay developed in our laboratory. The assay technique combines HPLC for separation of PGI₂ from its metabolites and radiochemical techniques achieving the great degree of sensitivity required for detecting blood levels.

Data Analysis

Hemodynamic data (i.e., blood pressure and pulse) were compared between the treated and untreated groups to verify initial comparability (t-test) and to detect changes over time (regression analysis and paired t-test). The rCBF, EEG, and infarct size data were analyzed using the Wilcoxon Rank Sum test. This non-parametric test does not assume normal distribution of the data and detects differences based on the ranks of the values rather than the values themselves.

Results

Hemodynamic Parameters

Mean arterial blood pressure data and mean pulse rates for the treated and untreated groups are presented in figures 1 and 2. In both groups, there was an overall significance level of 0.05 of a decreasing trend in pulse over the 6-hour occlusion period. This trend was less pronounced in the treated group. The arterial blood pressure showed an overall significance level of 0.05 of an increasing trend in the control animals but not in the PGI₂ treated animals. Hematocrit remained stable throughout each experiment with no significant differences among untreated and treated animals (33 ± 8% and 32 ± 9% respectively at the beginning of the experiment and 30 ± 8% and 33 ± 9% respectively at the beginning of the experiment and 30 ± 8% and 33 ± 9% respectively at the end of the experiment).

Regional Cerebral Blood Flow

The results of the 133Xe rCBF determinations are illustrated in figure 3. There was a pronounced decrease in rCBF in all animals upon occlusion of the MCA. This was followed by a smaller progressive improvement in rCBF throughout the period of ischemia. This improvement in rCBF was more prominent and achieved statistical significance only in the un-
treated group (p = 0.005 in the untreated animals, and p = 0.16 in the PGI2 treated animals).

EEG Analysis
The EEG background consisted of 5-30 Hertz activity of up to 100 μV as well as frequent bursts of 1-3 Hertz activity of up to 30 μV. In order to correct for bilaterally nonspecific voltage changes during the course of the experiments, the right and left amplitudes were compared. In 3 untreated animals and 2 PGI2 treated animals, pre-occlusion amplitudes were initially decreased by 33% or more on the right side as compared to the left. In all other animals, activity was initially symmetrical.

There was a 33% or greater reduction in amplitude over the right hemisphere in 5 control and 2 PGI2 treated animals immediately after occlusion. After 4 hours of occlusion this was present in 4 control and 3 treated animals. By 6 hours, 3 control and 2 treated animals had a 33% or greater reduction in right hemispheric amplitude. Taking each group as a whole, there were no significant differences between groups for each post-occlusion period. Moreover, intragroup variables were great.

Morphological Studies
(1) Gross Swelling
Ten animals in each group had grossly detectable right to left hemispheric shift. Among untreated animals, 6 had a midline shift between 0.5 and 1.0 mm, 2 animals had a midline shift between 1.0 and 1.5 mm, and 2 animals had a shift greater than 1.5 mm. In the treated group, 3 animals had a midline shift between 0.5 and 1.0 mm, 6 animals had a shift between 1.0 and 1.5 mm and one animal a midline shift greater than 1.5 mm. There were no statistically significant differences between the two groups.

(2) Extravasation of Dyes (Table 1)
The majority of animals in both treated and untreated groups showed diffuse extravasation of fluorescein after 6 hours of MCA occlusion. The fluorescein staining was present in both gray and white matter in the right MCA territory. Nine animals in the untreated group showed some degree of Evans blue staining in the right hemisphere, while only 4 animals in the PGI2 treated group showed such staining. The Evans blue staining was usually limited to gray matter areas.

(3) Carbon Filling
The grading of carbon filling defects (pallor zones) is summarized in table 2. There appeared to be no difference in obstruction to carbon filling among treated and untreated animals.

(4) Microscopic Findings
Severe ischemic neuronal alterations were present in the caudate nucleus and/or cortex supplied by the right MCA of 10 untreated and 11 PGI2 treated animals. The mean percentage of gray matter surface area with moderate or severe neuronal alterations was 47% in the untreated animals and 50% in the PGI2 treated animals. These were not statistically different when compared using the Wilcoxon Rank Sum test.

Sham Controls
Table 3 shows the mean blood pressures and rCBF determinations for the animals receiving PGI2 (n = 3) and buffer (n = 3) infusions without MCA occlusions. The blood pressure remained stable in all animals throughout the 6-hour infusion period. The rCBF remained relatively stable in the animals receiving buffered infusion, but dropped in the animals receiving PGI2 infusion. While the small number of animals did not allow statistical analysis, this trend was observed in all animals.

None of the brains showed extravasation of fluorescein or Evans blue, detectable lack of carbon filling, or midline shift. There were no ischemic neuronal alterations on microscopic examination.

Prostacyclin Pharmacokinetics
Figure 4 shows PGI2 concentrations in femoral venous blood during right intracarotid infusion of a tritium labeled PGI2 solution (100 ng/kg/min). The right MCA was clipped at the onset of the infusion. Signifi-

Table 1 Extravasation of Dyes in Brains of Untreated and PGI2 Treated Animals Six Hours After Right MCA Occlusion

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cent peripheral PGI$_2$ concentrations were detected within 5 minutes of the onset of infusion. Within 60 minutes, a plateau was reached.

**Discussion**

During the course of focal cerebral ischemia, a state of progressive microcirculatory impairment develops. Carbon perfusion studies demonstrate patchy non-perfused areas within the ischemic zone. These have been interpreted as a "no-reflow" phenomenon analogous to that seen in global ischemia. However, more recent investigations of erythrocyte and plasma transit time, and studies of collateral artery resistance, all indicate a progressive increase in microcirculatory resistance but persistence of microcirculatory flow during focal ischemia, despite the apparent lack of flow on carbon perfusion. Several mechanisms have been proposed to account for this phenomenon, including edema, vasospasm, and intravascular coagulation. While the significance of this microcirculatory impairment in causing or aggravating ischemic damage remains speculative, maintenance of microcirculation with mannitol or low molecular weight dextran appeared to decrease ischemic injury in animal studies.

Several indirect lines of evidence suggest that an imbalance in PGI$_2$, TXA$_2$, homeostasis may play a role in ischemic microcirculatory impairment. Free fatty acids including arachidonic acid are released in great quantities into the ischemic brain of various species. Under conditions of incomplete ischemia, or during re-perfusion after complete ischemia, there is also accumulation of cyclooxygenase products of arachidonic acid metabolism including vasoactive prostaglandins. No such accumulation occurs during complete ischemia, presumably because the enzyme cyclooxygenase requires small amounts of oxygen. Furthermore, Indomethacin and PGI$_2$, were found to prevent circulatory deficits during re-perfusion after complete generalized compression ischemia in dogs. While these observations have been recorded in generalized ischemia models, there are no analogous studies on focal cerebral ischemia.

The animal model of acute focal cerebral ischemia used in this investigation has been widely used by us and others. The events that follow experimental occlusion of the MCA in cats appear to resemble the neurologic and pathologic changes in acute major artery occlusion in humans.

In the present study, we chose intracarotid administration of PGI$_2$ to insure maximal delivery of this short-lived compound to the ischemic zone via collateral channels and to minimize its systemic side effects. The dosage used was similar to that employed by others in various animal models, and was, in our experience, the highest dosage not accompanied by hypotension. PGI$_2$ is stable in alkaline media, and at low temperatures. It was, therefore, kept on ice and infused in buffered saline at pH 10.5. Periodic assays of the infused solution insured that active PGI$_2$ was administered.

While PGI$_2$ (at this dosage) did not alter blood pressure in animals not undergoing MCA occlusion, it had a significant effect on the hemodynamic response during focal ischemia. The PGI$_2$ treated animals maintained stable mean arterial pressure throughout 6 hours of MCA occlusion, while untreated animals showed a significant progressive increase in arterial pressure during that period. A decrease in pulse rate was observed in all animals during the ischemic period, but untreated animals exhibited a more pronounced bradycardia. Since intracranial pressure was not monitored in this study, we cannot rule out an improvement in intracranial pressure in PGI$_2$ treated animals as the cause for these hemodynamic changes. However, di-
fect hemodynamic effects of PGI₂ appear a more likely cause in light of what is known about the systemic effects of this agent (i.e., diffuse vasodilation). Despite intracarotid infusion, our pharmacokinetic data indicates significant peripheral levels of PGI with this regimen. Interestingly, however, such PGI levels had no detectable hemodynamic effects on animals undergoing MCA occlusion.

Untreated animals had significant progressive improvement in rCBF during the 6-hour occlusion period. This may be due to the recruitment of new collateral channels, to hemodiluting effects of the intracarotid buffer infusion, or to the progressive increase in arterial pressure. PGI₂ treated animals showed no significant improvement in rCBF during the occlusion period.

Electroencephalographic changes in the ischemic border zone were not significantly different in the two groups. All animals exhibited a decrease in amplitude on the right side after MCA occlusion. This worsened gradually reaching a plateau after 3 to 4 hours. Some animals showed an improvement in EEG during the ischemic period. The findings in our study were similar to those of Hossman and Schuier, who also described a decrease in amplitude during focal ischemia rather than slow-wave activity.

Alterations of the blood-brain barrier permeability to vital dyes during focal ischemia has been described previously. There appears to be early leakage of fluorescein into the ischemic zone. Since fluorescein exists primarily in an unbound state, this is consistent with the breakdown of the blood-brain barrier to small molecules. Three to 6 hours after MCA occlusion, there is leakage of the protein-bound Evans blue dye into ischemic gray matter, suggesting a breakdown of the blood-brain barrier to large molecules. The leakage of Evans blue dye coincides with the onset of the "secondary phase" of ischemic edema. Current concepts of ischemic edema describe a "primary phase," associated predominantly with membrane pump failure, and a "secondary phase" with a lower rCBF threshold, coinciding with frank membrane disruption and breakdown of the blood-brain barrier to large molecules.

While fluorescein leakage was present in essentially all treated and untreated animals in this study, there appeared to be some protection against Evans blue leakage in our PGI₁ treated animals. Iannotti et al. suggested a role for prostaglandins in the late phase of ischemic edema in the gerbil, but not the early phase. Our findings are consistent with this hypothesis.

Progressive impairment of microcirculatory filling with carbon perfusion has been demonstrated previously in experimental models of acute focal cerebral ischemia. This was initially thought to represent a state of so-called "no-reflow." Subsequent studies have, however, indicated that the flow persists despite an increase in microcirculatory resistance. Carbon filling defects after 6 hours of MCA occlusion were similar in our untreated and PGI₁ treated animals.

Light and electron microscopic studies in fixative-perfused animals have clearly demonstrated the morphological changes in ischemic neurons, allowing the recognition and grading of such changes. These changes are distinct from the so-called "dark neurons" which are thought to result from inadequate fixation. In the present investigation, the tissue studied was well fixed by in vivo perfusion and later immersion. Ischemic changes were observed in all treated and untreated animals and were consistent with previous descriptions. The mean size of infarcts was not significantly different in untreated and PGI₁ treated animals.

The current investigation does not rule out an important role for the PGI₂-TXA₃ mechanism in focal cerebral ischemia. However, it demonstrates that within the limitations of our model and the number of animals used, intracarotid PGI₁ at the dosage used provided no beneficial effects on the electrical and morphological changes of focal cerebral ischemia. Furthermore, there is a possible compromise of rCBF in PGI₁ treated animals. Dye extravasation studies are, however, consistent with a possible protective effect of PGI₁ on the blood-brain barrier.

Several hypotheses can be proposed to explain the lack of improvement in ischemic injury by PGI₁. It is possible that endogenous PGI₁ released by the brain vasculature during ischemia provides the maximal beneficial effect this agent can contribute. Any additional PGI₁ may not be capable of overcoming other restrictions on microcirculation such as edema, vaso­spasm, or possible intravascular coagulation. Furthermore, while PGI₁ inhibits platelet synthesis of TXA₃, there may be other sources of TXA₃ and other prostaglandins involved in microcirculatory impairment.

Also, since PGI₁ and TXA₃ probably act on platelets and vascular walls via biochemically distinct receptors rather than by simple competition at a single receptor, excessive PGI₁ may not be capable of completely reversing the TXA₃ induced vasoconstriction and platelet aggregation. This is borne out by the study of Hal­lence and Furlow, where PGI₁ alone fail to prevent microcirculatory impairment when administered after the onset of global ischemia in dogs, while a combination of PGI₁ and Indomethacin alone fail to prevent microcirculatory impairment when administered after the onset of global ischemia in dogs, while a combination of PGI₁ and Indomethacin was beneficial. Inhibition of endogenous thromboxane synthesis (using indomethacin or selective TXA₃ synthetase inhibitors), in combination with intracarotid PGI₁, may prove to be a useful therapeutic modality in the future. Such experiments are currently in progress in our laboratory.

On the other hand, systemic hemodynamic effects of PGI₁ in the presence of impaired autoregulation may reduce collateral blood flow and offset any direct beneficial effects. PGI₁ may have on microcirculation or ischemic edema. This limitation may be overcome in future studies by decreasing the PGI₁ dosage or by combining hypertensive therapy with PGI₁ administration. As in all animal investigations, species variability may place additional restrictions on useful therapeutic conclusions.
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