The role of the prostacyclin-thromboxane system in cerebral vasospasm following induced subarachnoid hemorrhage in the rabbit


Department of Surgery, Division of Neurosurgery, and Department of Diagnostic Radiology, Vancouver General Hospital and University of British Columbia, and Division of Neurosurgery, Department of Surgery, Children's Hospital, Vancouver, British Columbia, Canada

Subarachnoid hemorrhage (SAH) was induced in 50 rabbits by injecting 1.25 cc/kg of autologous, well heparinized, fresh arterial blood into the cisterna magna, followed by suspending the animals in a head-down position at 30° for 15 minutes. The animals were evenly divided into five groups: a control group, or groups receiving post-SAH prostacyclin (PGI2), carbacyclin, thromboxane A2 (TXA2) synthetase inhibitor (OKY-1581), or nutralipid. Radiographic vertebrobasilar arterial spasm was demonstrated on the 3rd day post-SAH in the control animals. This was decreased in the prostacyclin and the carbacyclin groups and was absent in the OKY-1581 and the nutralipid groups. Cerebral blood flow (CBF) measurements on the 4th day post-SAH using the xenon-133 technique failed to reveal any significant difference between the prostacyclin, the carbacyclin, and the control groups, but flows in the nutralipid and the OKY-1581 groups were significantly higher. There was a good correlation between the clinical status and the CBF. Intracytoplasmic vacuolation and detachment of the vascular endothelium, seen ultrastructurally, may account for the impaired synthesis of prostacyclin. Exogenous prostacyclin and carbacyclin decreased vasospasm but failed to improve cerebral perfusion. OKY-1581 blocked the synthesis of the potent vasoconstrictor, TXA2, which is not only formed during platelet aggregation but also induces platelet aggregation. Nutralipid contains linolenic acid, a precursor of eicosapentaenoic acid (EPA), which is more potent in inhibiting platelet aggregation and in blocking TXA2 production. The various fatty acid constituents of nutralipid bind to albumin and thereby shorten the half-life of TXA2.

KEY WORDS cerebral vasospasm prostacyclin carbacyclin thromboxane A2 OKY-1581 nutralipid

Cerebral arterial spasm is a significant cause of mortality and morbidity in patients who suffer subarachnoid hemorrhage (SAH) from a ruptured intracranial aneurysm. The basic pathogenesis of the vasospasm is unclear. Numerous agents have been deemed responsible, including noradrenaline, 5-hydroxytryptamine (serotonin), erythrocytes, oxyhemoglobin, potassium, fibrin-fibrinogen degradation products, and an unidentified factor in the cerebrospinal fluid (CSF). A variety of drugs have been tested in experimental and clinical trials. So far, the results have been disappointing.

Recent advances in prostaglandin research provide an insight into its probable role in the pathogenesis of cerebral arterial spasm following SAH. This study examines the effects of prostacyclin (PGI2), carbacyclin, and a thromboxane A2 (TXA2) synthetase inhibitor, OKY-1581, on cerebral vasospasm, in particular on the spasm that occurs 24 hours or later following SAH. The correlation between the clinical status of the animal and the cerebral blood flow (CBF) has been investigated. The potential use of 20% nutralipid was also assessed.

Materials and Methods

Fifty New Zealand white rabbits of both sexes, each weighing between 1.7 and 2.6 kg, were used in this study. Ten animals were selected at random as controls. The remaining rabbits were evenly divided into four groups, receiving prostacyclin, carbacyclin, TXA2 synthetase inhibitor (OKY-1581), or nutralipid. All animals were maintained at 37°C by a heating pad. Intramuscular acepromazine maleate at 12.5 mg/kg was
used for premedication. An hour later, anesthesia was accomplished by intravenous administration of sodium pentobarbital at 20 mg/kg. The rabbits were allowed to breathe spontaneously in room air. One of the auricular arteries was catheterized. The blood pressure and Lead II of the electrocardiograph were monitored continuously by a Honeywell oscilloscope.*

A midline suboccipital incision centered over the foramen magnum was made and the neck muscles were dissected until the dura was visualized. Approximately 1.5 cc of CSF was removed and then fresh, autologous, well heparinized arterial blood (1.25 cc/kg) was injected into the cisterna magna over 20 seconds. To facilitate dispersion of the subarachnoid blood, the animals were placed in a head-down position on an inclined plane raised at 30° to the horizontal for 15 minutes. They were then transferred to the observation unit where the initial dose of the appropriate medication was given. The animals were examined after they awakened from the anesthesia and at least twice daily thereafter. For animals that developed respiratory arrest following SAH, mechanical ventilation was accomplished by a well fitted face mask and a Metomatic veterinary ventilator at 35 ml/kg and 12 to 14 breaths/min. Arterial blood gases were analyzed within 5 to 10 minutes after the resumption of spontaneous respiration.

Prostacyclin was prepared by dissolving 0.2 mg sodium prostacyclin in 30 cc of ice-cold, 50 mM Tris-saline buffer at pH 9.0. Within 30 minutes following SAH, 0.75 cc/kg (or 5 mcg/kg) of the prepared prostacyclin was given intravenously to each animal in the prostacyclin group. Thereafter the same dose was given intraperitoneally twice daily. Carbacyclin was prepared and administered to the animals in a similar manner except that the dose of carbacyclin was 10 times that of prostacyclin. Hence, each rabbit received 50 mcg/kg carbacyclin intravenously followed by 50 mcg/kg carbacyclin intraperitoneally twice daily. For the TXA2 synthetase inhibitor group, 15 cc of ice-cold normal saline was used to dissolve 3 gm OKY-1581. Within 30 minutes following SAH, 0.15 cc (or 30 mg) OKY-1581 was given intravenously. Thereafter, subcutaneous administration of 0.75 cc/kg (or 150 mg/kg) of the same medication was given once daily. The blood pressures were carefully monitored before, during, and for 45 minutes after the infusion of the medications. The prostacyclin (PGL2), carbacyclin, and OKY-1581 were all freshly prepared just prior to administration. Nutralipid (20%) was delivered to each of the 10 rabbits in the nutralipid group at 15 cc/kg (or 3 gm/kg) using an IVAC infusion pump through a femoral intravenous catheter. The same dose was first given immediately after SAH and then once daily at a rate of 15 cc/hr.

Cerebral angiography was performed in two animals selected at random prior to the induced SAH. The femoral artery was catheterized. Aortic arch study was performed using a No. 4 French catheter and 76% Conray solution. Subtraction films of the vertebral-basilar system were obtained. On the 3rd day following SAH, cerebral angiography was repeated in three animals from each of the control, prostacyclin, carbacyclin, OKY-1581, and nutralipid groups. Cerebral blood flow measurements using the xenon-133 (133Xe) technique were performed in 10 animals selected at random prior to the induction of SAH. This was repeated in all the surviving 45 animals on the 4th day following SAH. After dissection of the internal carotid arteries, intraarterial injection of 150 &mu Ci of 133Xe in 0.2 to 0.5 ml of sterile saline was accomplished in 2 to 3 seconds. The clearance of 133Xe from the brain was measured and recorded by the ADAC Laboratories Clinical Data System. Cerebral blood flow was calculated by the initial-slope index method as described by Waltz, et al.,39 as follows:

\[
\text{CBF (Fi)} = 6000 \lambda \frac{\log e^{-t}}{T_1 (sec)} (\text{ml/100 gm/min}),
\]

where \( \lambda \) = partition coefficient for xenon between blood and brain, and \( T_1 \) = time required for the recorded counting rate of the clearance curve to decrease from the maximum to one-half the maximum. Chi-square testing was used for statistical analysis.

On the 5th day following SAH, the animals were perfused by intracardiac injection of 5% glutaraldehyde in 0.1 M sodium cacodylate buffer (pH 7.4) using 200 cc/animal. The brains and the cervical cords of all the surviving 45 animals were removed en bloc. The basal cisterns, and the vertebral, basilar, and posterior cerebral arteries were covered by clotted blood. The basilar arterial segments from four animals of each group were removed and examined ultrastructurally. The light microscopy segments were processed in paraffin and stained with hematoxylin and eosin (H & E), and Verhoeff’s elastica van Giesen. The portions for electron microscopy were rinsed in 0.1 M sodium cacodylate buffer, fixed in 1% osmium tetroxide and 5% uranyl acetate, dehydrated in a graded series of ethanol to absolute ethanol, embedded in 100% epoxy resin, stained with lead citrate, and examined with a Philips EM 400 transmission electron microscope.

**Results**

**Physiological Parameters**

Respiratory arrest occurred in eight out of the 10 animals in each of the five groups of animals either immediately or within 5 minutes of induction of SAH. The duration of apnea ranged from 8 seconds to a full minute, with a mean of 25 seconds. There was no significant variation in the period of apnea among

---

*Oscilloscope, Model PM-2A, manufactured by Honeywell Medical Electronics, 1 Campus Drive, Pleasantville, New York.
FIG. 1. Cerebral angiograms in the control group. A: Before subarachnoid hemorrhage (SAH), the vertebrobasilar system was well demonstrated. B: On the 3rd day post-SAH, there was poor visualization of both the distal vertebral and the proximal basilar arteries (arrow) secondary to vasospasm.

TABLE 1
Morbidity and mortality in each treatment group of 10 rabbits

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control</th>
<th>OKY-1581</th>
<th>Carbacyclin</th>
<th>PG12</th>
<th>Nutralip</th>
</tr>
</thead>
<tbody>
<tr>
<td>death</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1*</td>
</tr>
<tr>
<td>transient hemiparesis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>drowsiness &amp; lethargy</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

* One died acutely following cerebral angiography.

the five different groups. Arterial blood gases measured 5 to 10 minutes after the resumption of spontaneous respiration were all within normal limits (pH 7.35 to 7.40, pO2 70 to 100 mm Hg, and pCO2 35 to 40 mm Hg).

The heat rate of the animals prior to SAH was 170 ± 30 beats/min. It dropped to 130 ± 30 beats/min within 20 seconds after injection of blood into the subarachnoid space, but rose gradually to the preinjection level within 5 to 10 minutes. Cardiac arrhythmias including ST segment depression, T wave inversion, sinus bradycardia, nodal rhythm, and premature ventricular contractions were observed in 70% of the animals within 5 seconds after injection of blood into the cisterna magna. The electrocardiographic recordings reverted back to normal in all the animals within 10 minutes.

The mean arterial blood pressure displayed by the Honeywell oscilloscope prior to the induced SAH was 90 ± 8 mm Hg. Following the insult, a dramatic increase in the systemic blood pressure to a mean of 160 ± 25 mm Hg occurred. Gradually, it returned to the preinjection level within 4 to 6 minutes.

Following intravenous administration of prostacyclin, the mean blood pressure decreased almost instantaenously from 90 ± 8 to 60 ± 10 mm Hg and remained low throughout the period of infusion. However, it returned to baseline within a minute following the termination of the drug infusion. When prostacyclin was delivered to the rabbits intraperitoneally, the decline in blood pressure was delayed for 30 seconds and reached a low of 75 ± 10 mm Hg. However, it remained low for 20 minutes after the drug had been stopped. A similar blood pressure response was obtained in the carbacyclin group, except that the drop was less impressive and reached a low of 75 ± 10 mm Hg following intravenous carbacyclin administration and 80 ± 10 mm Hg after it was given intraperitoneally. After intraperitoneal injection of carbacyclin, 30 minutes passed before the blood pressure returned to the preinjection level. There was no recorded change in the mean blood pressure after OKY-1581 injection, either intravenously or subcutaneously. A slight increase of 3 to 7 mm Hg was found during intravenous infusion of nutralipid.

Clinical Observations

One animal in each of the control and prostacyclin groups died 15 to 30 minutes following the SAH. Autopsy revealed diffuse SAH, most prominent around the brain stem region with blood in the Sylvian fissures and basal cisterns, and clotted blood covering the posterior cerebral, basilar, and vertebral arteries. Another control animal demonstrated dense right hemiparesis on the 1st day post-SAH but this resolved spontaneously within 24 hours. On the 2nd day post SAH, one further animal in the prostacyclin group died. One rabbit from each of the control and the nutralipid groups died immediately following cerebral angiography. Of the 45 animals that survived, six rabbits in the
Prostacyclin-thromboxane system in vasospasm

Cerebral angiography performed prior to SAH demonstrated the vertebrobasilar system well (Fig. 1A). The diameter of the basilar artery in the baseline film was taken as 100%. On the 3rd day following SAH, repeat cerebral angiography revealed vasospasm in the control animals. The distal portions of both vertebral arteries and the proximal segment of the basilar artery were poorly visualized as a result of cerebral arterial spasm (Fig. 1B). The average diameter of the basilar artery was 45% of baseline (Fig. 2). Vasospasm was less pronounced in the prostacyclin and carbacyclin groups (Fig. 3). The average constriction of the basilar arteries for these groups was 40% and 25% of the control diameter, respectively (Fig. 2). There was no significant change in the size of the basilar artery between the pre-SAH baseline diameter and the post-SAH OKY-1581 and nutralipid group diameters (Fig. 4).

Cerebral Blood Flow Studies

The mean CBF obtained in 10 animals selected at random prior to the SAH was 88.9 ml/100 gm/min. The results of the CBF study performed on the 4th day post-SAH in all the 45 surviving animals are shown in Table 2. There was good correlation between the clinical status of the animals and their CBF results. Low CBF values were found only in the animals that were drowsy and lethargic. No significant difference in the CBF between the prostacyclin, the carbacyclin, and the control groups was noted. On the other hand, the CBF obtained in the OKY-1581 and the nutralipid groups were significantly higher than those in the control group (p < 0.02 and p < 0.01, respectively).

Pathological Findings

At autopsy, diffuse resolving SAH was seen most prominently over the ventral brain stem and the basal cisterns. The posterior cerebral, basilar, and vertebral arteries were completely covered by clotted blood. Light microscopy using H & E and elastica van Gieson stains failed to reveal any abnormalities involving the tunica intima, the internal elastic lamina, and the tunica media. This applied to both the clinically active and the drowsy rabbits. Ultrastructurally, there was extensive “intracytoplasmic vacuolation” and frequent detach-

---

TABLE 2

CBF obtained on 4th day post-SAH in 45 surviving rabbits according to treatment group*

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Control (n = 8)</th>
<th>OKY-1581 (n = 10)</th>
<th>Carbacyclin (n = 10)</th>
<th>PGI2 (n = 8)</th>
<th>Nutralipid (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF (ml/100 gm/min)</td>
<td>77.4</td>
<td>81.1</td>
<td>92.9</td>
<td>83.9</td>
<td>83.9</td>
</tr>
<tr>
<td>85.3</td>
<td>92.9</td>
<td>67.9</td>
<td>69.4</td>
<td>79.2</td>
<td></td>
</tr>
<tr>
<td>62.0†</td>
<td>87.4</td>
<td>64.0†</td>
<td>70.8†</td>
<td>83.9</td>
<td></td>
</tr>
<tr>
<td>59.4†</td>
<td>85.3</td>
<td>66.4†</td>
<td>73.9</td>
<td>114.7</td>
<td></td>
</tr>
<tr>
<td>67.9†</td>
<td>97.8</td>
<td>79.2</td>
<td>67.9†</td>
<td>104.0</td>
<td></td>
</tr>
<tr>
<td>66.5†</td>
<td>76.4</td>
<td>97.8</td>
<td>77.5</td>
<td>87.5</td>
<td></td>
</tr>
<tr>
<td>58.4†</td>
<td>85.3</td>
<td>72.3</td>
<td>66.4†</td>
<td>87.5</td>
<td></td>
</tr>
<tr>
<td>67.9†</td>
<td>87.5</td>
<td>64.0†</td>
<td>62.0†</td>
<td>89.9</td>
<td></td>
</tr>
<tr>
<td>92.4</td>
<td>89.9</td>
<td>108.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>89.9</td>
<td>76.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>68.0‡</td>
<td>87.6‡</td>
<td>77.2‡</td>
<td>71.4‡</td>
<td>93.3‡</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.02 (p > 0.2) (p > 0.5) (p < 0.01)

† Clinically drowsy and lethargic.
‡ Mean CBF of each group, with significance of difference from control values.
R. C. Chan, et al.

FIG. 5. Transmission electron micrographs in control group animals; transverse sections. A: Extensive "intracytoplasmic vacuolation" is seen. x 2280. B: There are frequent detachments of the endothelial cells from one another and from the internal elastic lamina. x 4320.

...ment of the endothelial cells from one another and from the internal elastic lamina in the basilar arteries of the control group animals (Fig. 5). In the tunica media, a moth-eaten appearance of the muscle cells with variation in cytoplasmic densities was frequently present. The vessels of the prostacyclin and the carbacyclin groups demonstrated less extensive degenerative changes (Fig. 6), while those belonging to the nutralipid and the OKY-1581 groups were normal ultrastructurally (Fig. 7).

FIG. 6. Transmission electron micrographs, transverse sections, showing mild to moderate degrees of "intracytoplasmic vacuolation" and endothelial detachments. A: Prostacyclin group section, x 2600. B: Carbacyclin group section, x 5600.
Prostacyclin-thromboxane system in vasospasm

Discussion

Prostacyclin is a powerful vasodilator. It is the most potent endogenous inhibitor of platelet aggregation known. Its sodium salt is water-soluble. At acid pH, it rapidly hydrolyzes into 6 keto-prostaglandin (PG)F_{1α}. At pH 7.48 and 25°C, its half-life is between 3½ and 10½ minutes. The ability of prostacyclin to relax isolated baboon, canine, and human cerebral arteries has been reported. In this study, the angiographic spasm is decreased in the prostacyclin group as compared to that of the control group (Fig. 2). Prostacyclin is generated from arachidonic acid and/or prostaglandin endoperoxide by human cerebral arteries. The rate of synthesis is highest in the vascular endothelium and decreases toward the adventitial surface. Following SAH, the synthetic activity of prostacyclin in the cerebral arteries decreases especially between Day 3 and Day 8. This is thought to be responsible, at least in part, for the cerebral vasospasm. The extensive intracytoplasmic vacuolation and frequent detachment of the basilar endothelial cells from one another and from the internal elastic lamina, seen ultrastructurally in the control animals, may account for the impaired synthesis of prostacyclin (Fig. 5).

Endogenous cerebral prostacyclin functions as a local or tissue hormone and plays a minor role in the direct regulation of systemic blood pressure. Exogenous prostacyclin, however, decreases systemic blood pressure in a dose-related manner. In this study, intravenous administration of 5 μg/kg of prostacyclin resulted in a 30-mm Hg decrease in the mean blood pressure. Whether the transient drop in systemic blood pressure is related to the low perfusion value achieved by the animals in the prostacyclin and carbacyclin groups is unclear.

Carbacyclin is a stable analog of prostacyclin. It has a similar spectrum of activity as prostacyclin, but is only one-tenth as potent in inhibiting platelet aggregation and in dilating the peripheral vessels. The decline in blood pressure produced by carbacyclin is less than that produced by an equally effective anti-aggregatory dose of prostacyclin because carbacyclin produces a greater increase in the cardiac output. There was some improvement in the CBF obtained from the animals that received carbacyclin as compared to the controls (Table 2), but the difference is not statistically significant (p > 0.5).

The conversion of cyclic endoperoxides PGG_{2} and PGH_{2} to TXA_{2} is the preferential metabolic pathway in human platelets and brain with PGE_{2}, PGF_{2}, and PGD_{2} being minor metabolic products (Fig. 8). Thromboxane A_{2} is a powerful vasoconstrictor. It is not only released during platelet aggregation but also induces platelet aggregation. The aggregation of platelets is responsible for the release of serotonin (5-hydroxytryptamine), which is thought to be responsible for the acute phase of cerebral vasospasm following SAH. The vascular tone is probably controlled by a delicate balance between prostacyclin and TXA_{2}. Following SAH, the synthesis of prostacyclin is considerably decreased. This upsets the balance and favors the vasoconstrictor, TXA_{2}, which is already a preferential product in the prostaglandin synthetic pathway. In addition, platelet aggregation following SAH releases multiple chemicals including TXA_{2} and serotonin.
Thromboxane A₂ induces further platelet aggregation and sets up a vicious cycle. This sequence of events is probably responsible, at least in part, for the cerebral vasospasm. The TXA₂ synthetase inhibitor, OKY-1581, relieves arterial spasm by blocking the production of TXA₂, and thereby inhibits platelet aggregation and the release of serotonin.

In 1982, Sasaki, et al., reported the effectiveness of OKY-1581 in relieving angiographic spasm following induced SAH in dogs. The lack of perfect correlation between the clinical status and the angiographic spasm is a well recognized phenomenon; however, good correlation between the neurological examination and CBF was obtained in this model. The result in this study confirms not only clinically and angiographically, but also by CBF analysis the effectiveness of the TXA₂ synthetase inhibitor, OKY-1581, in relieving cerebral arterial spasm. It also provides further evidence of the good correlation between the clinical status of the animals and their CBF values. OKY-1581 is a stable watersoluble product. It can be given orally, subcutaneously, or intravenously. Following oral or subcutaneous administration, its effect lasts for 24 to 48 hours.

Clinically and angiographically, the animals in the nutralipid group performed well. There was significant improvement in their CBF results as compared to those in the control group (p < 0.01). The slight increase in blood pressure and the volume of infusate (15 cc/kg/day) improved cerebral perfusion, but were probably not enough to account for such a significant difference.

The composition of 20% nutralipid is shown in Table 3. The major fatty acid components are oleic, linoleic, linolenic, and arachidonic acids (Table 4). Linoleic acid, an essential polyunsaturated, is converted by elongation and desaturation to arachidonic acid. However, the conversion of linoleic acid to arachidonic acid is blocked by linolenic acid, which is also the precursor of eicosapentaenoic acid (EPA). While arachidonic acid, PGG₂, PGH₂, and TXA₂ induce platelet aggregation, oleic acid, linoleic acid, linolenic acid, and EPA inhibit it; however, EPA is more potent than its precursor, linolenic acid, in inhibiting platelet aggregation and in blocking TXA₂ synthesis. This may be caused by the rapid occupancy of TXA₂ and PGH₂ "receptors" on the platelet membrane and by the slow displacement of arachidonic acid from platelet phospholipid by EPA. According to Dyerberg, et al., EPA also gives rise to another prostacyclin, possibly PGI₁, which has similar anti-aggregating and vasodilating properties to those of prostacyclin (PGI₂). The half-life of TXA₂ is 30 seconds at 37°C. It is bound to albumin by non-covalent bonding. After coating the albumin with fatty acids, Lagarde, et al., found significant shortening of the half-life of TXA₂. Nutralipid, therefore, improves cerebral perfusion by blocking the production of TXA₂, by shortening its half-life, and possibly by inducing the formation of local vasodilating hormone PGI₂.

Pathologically, Weir, et al., reported no significant histological abnormalities in the cerebral blood vessels of monkeys following induced SAH. A similar result was encountered in this study. In 1978, Mayberg, et al., failed to find any ultrastructural abnormalities in the feline basilar artery following SAH. However, Tanabe, et al., found endothelial detachment and intracytoplasmic vacuolation of basilar endothelial cells as well as a moth-eaten contour of the smooth-muscle cells in the tunica media of the dog's basilar artery, 3 to 7 days following SAH. These changes were present in the basilar arteries of the control group of rabbits in this study. The reported intracytoplasmic vacuoles in the smooth-muscle cell layer were not seen here, but there were frequent variations in the cytoplasmic densities of the smooth-muscle cells. The significance of these changes in the tunica media of the basilar arteries is unclear. Frank necrosis and the appearance of

![Diagram of prostaglandin (PG) and thromboxane (Tx) biosynthesis in the platelets.](image)

**TABLE 3**

<table>
<thead>
<tr>
<th>Contents</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>soybean oil</td>
<td>200 gm</td>
</tr>
<tr>
<td>fractionated egg phospholipids</td>
<td>12 gm</td>
</tr>
<tr>
<td>glycerin USP</td>
<td>22.5 gm</td>
</tr>
<tr>
<td>energy</td>
<td>2000 kcal</td>
</tr>
</tbody>
</table>

**TABLE 4**

<table>
<thead>
<tr>
<th>Contents</th>
<th>Soybean Oil</th>
<th>Egg Phospholipids</th>
</tr>
</thead>
<tbody>
<tr>
<td>oleic acid</td>
<td>26.5%</td>
<td>32%</td>
</tr>
<tr>
<td>linoleic acid</td>
<td>50%</td>
<td>12.5%</td>
</tr>
<tr>
<td>linolenic acid</td>
<td>8.5%</td>
<td>0</td>
</tr>
<tr>
<td>arachidonic acid</td>
<td>0</td>
<td>4.2%</td>
</tr>
</tbody>
</table>
Prostacyclin-thromboxane system in vasospasm

“plump cells” in the tunica media reported by Hughes and Schianchi were not found in this study.

Conclusions

The prostacyclin-thromboxane system plays an important role in the pathogenesis of cerebral arterial spasm following SAH. Prostacyclin (PGI₂) and carba-cyclin decrease vasospasm, but fail to improve cerebral perfusion. The thromboxane A₂ synthetase inhibitor, OKY-1581, and 20% nutralipid cause clinical improvement by relieving the arterial spasm and increasing the CBF. There is good correlation between the clinical status of the animals and their CBF values. The basis for the beneficial effect of nutralipid in the management of cerebral vasospasm following SAH has been discussed.

Acknowledgments

We would like to express our gratitude to Dr. C. L. Dolman, Dr. John E. Pike, Dr. K. Berry, Dr. R. Morrison, Dr. D. Lyster, Dr. K. Leighton, Dr. B. MacLeod, Dr. G. Quamme, Miss G. Medernach, Ms. D. Wobma, Mrs. E. Chang, Ms. B. Lyster, Dr. K. Leighton, Dr. B. MacCleod, Dr. G. Quamme, Dr. John E. Pike, Dr. K. Berry, Dr. R. Morrison, Dr. D. McLintock, Mr. M. Tsuboshima, Mr. Mizuta, Mr. T. McLintock, Mr. G. Leung, and Mr. R. Van Dyke for their assistance in the research and the preparation of this paper.

References

34. Szczeklik A, Gryglewski RJ, Nizankowski R, et al: Circulatory and anti-platelet effects of intravenous prosta-
36. Tanishima T: Cerebral vasospasm: contractile activity of hemoglobin in isolated canine basilar arteries. J Neuro-
surg 53:787–793, 1980
37. Toda N, Shimizu K, Ohta T: Mechanism of cerebral arterial contraction induced by blood constituents. J Neuro-
surg 53:312–322, 1980
38. Vane JR, McGiff JC: Possible contributions of endoge-

Manuscript received June 2, 1983.
Accepted in final form June 25, 1984.
This work was supported by the Vancouver Research Foundation.
Address reprint requests to: Felix A. Durity, M.D., 910 West 10th Avenue, 3rd Floor, Room 3100, Vancouver, British Columbia, V5Z 4E3, Canada.