Model of Electrocardiographic Changes Seen With Subarachnoid Hemorrhage in Rabbits

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We developed a new method for introducing drugs into the basal cistern of rabbits. With minimal surgical invasion, we used either the opening of the craniopharyngeal duct to access the chiasmatic cistern or the suture between the basisphenoid and basioccipital bones to access the interpeduncular cistern. With our method, 0.5 ml contrast medium injected into three rabbits was determined roentgenographically to remain in the basal cistern; histologically, all the brain tissue remained intact. Intracisternal injection of 0.5 ml physiological saline into five rabbits had no effect on the cardiovascular system. In 23 rabbits, injection of 0.5 ml 0.1% prostaglandin F\(_2\alpha\) led to a wide variety of electrocardiographic changes, including sinus bradycardia (in 43.5%), premature atrial contractions (in 17.4%), and premature ventricular contractions (in 39.1%). In 15 rabbits with severe changes, arrhythmia was followed by ST depression (in 30.4%), ST elevation (in 8.7%), T wave inversion (in 4.3%), ventricular tachycardia (in 17.4%), or ventricular fibrillation (in 4.3%). Intracisternal injection of 0.5 ml 1.0% lidocaine into the 23 rabbits was very effective in overcoming bradycardia and arrhythmias. We conclude that the clinical features of electrocardiographic changes seen in patients with subarachnoid hemorrhage are reproducible in this rabbit model. (Stroke 1989;20:112–118)

Drugs have been introduced into the basal cistern of cats, rabbits, and monkeys using transclival\(^1-^3\) or transorbital\(^4-^6\) approaches. However, these methods are excessively invasive, bleeding is often difficult to control, and the cisterns are not always reached. We designed two new approaches to reach the basal cistern, through an opening in the craniopharyngeal duct or through the suture between the basisphenoid and basioccipital bones, with minimal surgical injury. Intracisternal injection of 0.5 ml 0.1% prostaglandin F\(_2\alpha\) (PGF\(_2\alpha\)) produced severe electrocardiographic (ECG) changes resembling those seen in patients with subarachnoid hemorrhage.

Materials and Methods

We anesthetized 48 domestic rabbits weighing 2.0–2.5 kg with ether and placed a venous line in an ear vessel. Each rabbit was fixed supine, a tracheostomy was performed, and ventilation through the tracheostomy tube was maintained with a Harvard small animal respirator (South Natick, Massachusetts). During surgery each rabbit was anesthetized with ether and immobilized with pancuronium bro-
firming that the CSF could be aspirated, 0.3 ml 0.1% PGF₂α was injected into the thoracic subarachnoid space. In five rabbits, 0.5 ml 0.1% PGF₂α was injected into the venous line in the ear.

A few rabbits were placed supine with their heads fixed so that the ventral surface of the basisphenoid bone was practically horizontal, and amidotrizoate meglumine, a radiopaque medium, was injected into the chiasmatic cistern (Figure 2) or the interpeduncular cistern. Roentgenograms showed that when 1.0 ml contrast medium was injected it entered the cervical subarachnoid space; however, when 0.5 ml was used, the contrast medium remained in the region of the basal cistern.

Each rabbit was then killed; the skull was removed and placed in 10% buffered formalin for several days, decalcified, sectioned, and stained with hematoxylin and eosin. With either approach (through

**FIGURE 1. Anatomy of rabbit skull.**

**FIGURE 2. Lateral view, roentgenogram of rabbit skull showing 0.5 ml radiopaque contrast medium (amidotrizoate meglumine) injected through orifice of craniopharyngeal duct into chiasmatic cistern. Contrast medium appeared in basal cistern but did not extend into cervical subarachnoid space.**
FIGURE 3. Photomicrograph, injection site in rabbit skull of opening of craniopharyngeal duct (arrow) and chiasmatic cistern. Hemorrhage is seen in duct and subarachnoid space, but pituitary gland and brain tissue is intact. Hematoxylin and eosin stain, ×80.

the craniopharyngeal duct into the chiasmatic cistern [Figure 3] or through the suture between the basisphenoid and basisoccipital bones into the interpeduncular cistern [Figure 4] microscopy showed slight hemorrhage at the injection site and in the subarachnoid space. The brain tissue, including the pituitary gland, was intact.

The data are presented as mean±SD. We compared groups of five rabbits each before injection of 1.0 or 0.5 ml physiological saline using analysis of variance; within each group the significance of changes in physiological parameters were evaluated using Student's t test for paired samples, and between groups Student's t test for unpaired samples was used to compare postinjection values. We compared rates of occurrence of ECG changes produced by injections of two volumes of two concentrations of PGF$_{2\alpha}$ into four sites between groups using the $\chi^2$ test. All differences were considered significant when $p<0.05$.

Results

In 10 rabbits, hematocrit was measured by the centrifuge method. The hematocrits before surgery and immediately after injection of physiological saline into the basal cistern were 33.2±0.2% and 31.4±0.4% for chiasmatic and interpeduncular cistern injections, respectively.

Table 1 shows that injection of 1.0 ml physiological saline into the chiasmatic cistern significantly elevated systolic and diastolic blood pressure after 5–15 minutes, whereas injection of 0.5 ml physiological saline produced no change except at 5 minutes; heart rate remained unchanged. pH, Paco$_2$, PaO$_2$, base excess, total protein, and serum Na$^+$ and K$^+$ concentrations remained unchanged when 0.5 ml physiological saline was injected into the chiasmatic cistern.

As shown in Table 2, intracisternal injection of 0.5 ml 0.1% PGF$_{2\alpha}$ induced ECG changes in 90–100% of the rabbits (Groups V and II), while 0.3 ml 0.1% PGF$_{2\alpha}$ induced ECG changes in 50–60% (Groups III and VI); the difference between volumes injected into the chiasmatic cistern (Groups II and III) was significant. Intracisternal injection of 0.3 ml 0.01% PGF$_{2\alpha}$ (Group VII) produced no ECG changes. After the C$_{1-2}$ had been dissected (Group IV), injection of 0.5 ml 0.1% PGF$_{2\alpha}$ into the chiasmatic cistern produced no ECG changes. Injection of 0.3 ml 0.1% PGF$_{2\alpha}$ into the thoracic subarachnoid...
space produced no ECG changes in any rabbit (Group VIII). Intravenous injection of 0.5 ml 0.1% PGF$_2$A did not cause any ECG changes (Group IX), and the degree of bradycardia was slight.

The wide variety of ECG changes produced by intracisternal injection of 0.5 ml 0.1% PGF$_2$A are shown in Table 3. In 10 of 23 rabbits (43.5%), sinus bradycardia occurred, but blood pressure did not change. The time to onset of bradycardia was 38.6±22.9 seconds; after between 20 seconds and 4 minutes 40 seconds, atrial or ventricular premature contractions appeared (Figure 5). These arrhythmias were (in 15 severe cases) followed by T wave inversion, ST elevation, or ventricular tachycardia. In one rabbit, ventricular fibrillation occurred, followed by cardiac arrest.

Intracisternal injection of 0.5 ml 1.0% lidocaine was very effective in correcting the ECG changes caused by intracisternal injection of PGF$_2$A. Five to eighty seconds (mean±SD 28.7±29.4 seconds) after the injection of lidocaine, the bradycardia or arrhythmias disappeared, and thereafter the changes in ST and T waves gradually reverted to normal (Figure 6).

**Discussion**

ECG changes commonly seen in patients with acute subarachnoid hemorrhage usually mean impending heart damage, especially myocardial infarction. Since the reports of Burch et al. and Connor, a number of studies on ECG abnormalities have appeared. Nevertheless, effective treatment to improve the ECG changes has not been established. Elucidation of the mechanism of ECG

**Table 1. Changes in Blood Pressure and Heart Rate in Rabbits Following Injection of Physiological Saline Into Chiasmatic Cistern**

<table>
<thead>
<tr>
<th>Volume of saline</th>
<th>1.0 ml (n=5)</th>
<th>0.5 ml (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (torr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>104.0±2.9</td>
<td>120.0±8.5</td>
</tr>
<tr>
<td>5 min</td>
<td>127.6±8.1*</td>
<td>120.6±9.0f</td>
</tr>
<tr>
<td>10 min</td>
<td>133.0±9.8*</td>
<td>120.0±7.3f</td>
</tr>
<tr>
<td>15 min</td>
<td>129.0±10.4</td>
<td>126.6±6.9</td>
</tr>
<tr>
<td>Diastolic (torr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>68.4±2.8</td>
<td>87.0±7.7</td>
</tr>
<tr>
<td>5 min</td>
<td>85.4±8.1*</td>
<td>89.4±9.1f</td>
</tr>
<tr>
<td>10 min</td>
<td>93.4±8.5*</td>
<td>90.0±9.6f</td>
</tr>
<tr>
<td>15 min</td>
<td>84.0±8.9*</td>
<td>89.6±7.3</td>
</tr>
<tr>
<td>Heart rate (min$^{-1}$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>246.0±15.0</td>
<td>231.2±11.8</td>
</tr>
<tr>
<td>5 min</td>
<td>232.0±15.0</td>
<td>220.8±15.6*</td>
</tr>
<tr>
<td>10 min</td>
<td>236.8±14.0</td>
<td>226.8±18.4</td>
</tr>
<tr>
<td>15 min</td>
<td>238.4±19.0</td>
<td>226.4±18.6</td>
</tr>
</tbody>
</table>

Data are mean±SD.

*p<0.05 different from before, Student’s paired t test.

$*$p<0.025, 0.05 different from 1.0 ml, Student’s unpaired t test.
changes and establishment of adequate treatment requires further attention.

Our first objective was to investigate a less invasive and more accurate method of introducing drugs into the basal cisterns of rabbits. In species such as cats or rabbits, the basal cisterns are very small. In rabbits, the distance between each side of the clinoid process of the basisphenoid bone is only 2.0 mm. In addition, the cisterns are surrounded by rich vessels, and an inappropriate approach can lead to bleeding. A transclival approach is even more invasive. In contrast, our method is accurate and less invasive. One drawback in treating the median vertebral vein is that it easily ruptures and bleeds. We found that by injecting a small amount of Biobond (0.07 g cyanoacrylate monomer, 0.07 g nitrile rubber, and 0.01 g toluene diisocyanate in 1 ml) into the vessel, the problem could be overcome with no untoward effect on the cardiovascular system.11,12

Our second aim was to select a drug that, when introduced into the basal cistern, would produce ECG changes similar to those seen in patients with acute subarachnoid hemorrhage. In animal experiments, cerebral vasospasm has been generally produced by oxyhemoglobin, serotonin, PGF\textsubscript{2\alpha}, thrombin, KCl, or epinephrine. Preliminary investigation of intracisternal injection of serotonin or epineph-

TABLE 2. Changes in Electrocardiogram in Rabbits Produced by Injection of PGF\textsubscript{2\alpha}.

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>Volume (ml)</th>
<th>n</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no.</td>
</tr>
<tr>
<td>Chiasmatic cistern</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Normal saline</td>
<td>0.5</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>0.1% PGF\textsubscript{2\alpha}</td>
<td>0.5</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>III</td>
<td>0.1% PGF\textsubscript{2\alpha}</td>
<td>0.3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>IV*</td>
<td>0.1% PGF\textsubscript{2\alpha}</td>
<td>0.5</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Interpeduncular cistern</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>0.1% PGF\textsubscript{2\alpha}</td>
<td>0.5</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>VI</td>
<td>0.1% PGF\textsubscript{2\alpha}</td>
<td>0.3</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>VII</td>
<td>0.01% PGF\textsubscript{2\alpha}</td>
<td>0.3</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Thoracic subarachnoid space</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIII</td>
<td>0.1% PGF\textsubscript{2\alpha}</td>
<td>0.3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Intravenous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IX</td>
<td>0.1% PGF\textsubscript{2\alpha}</td>
<td>0.5</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

PGF\textsubscript{2\alpha}, prostaglandin F\textsubscript{2\alpha}.
*Ci\textsubscript{2} was dissected.
†p<0.05 different from Group I, χ\textsuperscript{2} test.
‡Significantly different from Group III.
§Not different from Group VI.

TABLE 3. Electrocardiographic Effects of Intracisternal Injection of 0.5 ml 0.1% Prostaglandin F\textsubscript{2\alpha} and 0.5 ml 1.0% Lidocaine Into 23 Rabbits

<table>
<thead>
<tr>
<th>Type</th>
<th>Arrhythmia</th>
<th>Positive effects of lidocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>%</td>
</tr>
<tr>
<td>All rabbits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>10</td>
<td>43.5</td>
</tr>
<tr>
<td>Premature beats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraventricular</td>
<td>4</td>
<td>17.4</td>
</tr>
<tr>
<td>Ventricular</td>
<td>9</td>
<td>39.1</td>
</tr>
<tr>
<td>Rabbits with severe changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST depression</td>
<td>7</td>
<td>30.4</td>
</tr>
<tr>
<td>ST elevation</td>
<td>2</td>
<td>8.7</td>
</tr>
<tr>
<td>T inversion</td>
<td>1</td>
<td>4.3</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>4</td>
<td>17.4</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>1</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Chiasmatic cistern in 13, interpeduncular cistern in 10 rabbits. *% of number of rabbits with arrhythmias.

FIGURE 5. Electrocardiographic effect of intracisternal injection of 0.5 ml 0.1% prostaglandin F\textsubscript{2\alpha} in rabbits.
LIDOCAINE (1.0%/0.3ml)

before

1'30"

3'00"

before

10"

Figure 6. Effect of intracisternal injection of 0.5 ml 1.0% lidocaine on electrocardiographic changes produced by 0.5 ml 0.1% prostaglandin E2.

Rine led to severe arrhythmias and unreliable results. Intracisternal injection of 0.3 or 0.5 ml 1.0% PGF2α led to a wide variety of ECG changes similar to those seen in patients with subarachnoid hemorrhage. Our results suggest that these ECG changes were not due to an absorption of the drug into the circulation or to a direct stimulatory effect on the thoracic subarachnoid sympathetic nerves.

The mechanism of ECG changes is considered to relate to a massive release of catecholamine, stimulation of the sympathoadrenal system or the sympathetic cardiac nerve, stimulation of the hypothalamus due to cerebral vasospasm. Locally applied PGF2α produces cerebral vasospasm, but further studies on the mechanism of ECG changes produced by intracisternal injection of PGF2α are required. Intracisternal injection of 1.0% lidocaine immediately abolished the ECG changes produced by intracisternal injection of PGF2α. However, the mechanism of this antiarrhythmic effect was not clear.

We conclude that the clinical features of ECG changes seen in patients with subarachnoid hemorrhage are reproducible in this animal model and that therapeutic aspects of drug administration may be tested using this method.

References

KEY WORDS • electrocardiography • subarachnoid hemorrhage • rabbits
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