Extracranial-Intracranial Bypass in Experimental Cerebral Infarction in Dogs

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SUMMARY Unilateral permanent occlusion of the proximal part of the middle cerebral artery (MCA) was performed in 24 dogs. End-to-side anastomosis of the maxillary artery (MA) and a branch of the MCA on the occluded side was made 4 hours later in 8 dogs (prompt bypass group), and 3 weeks later in 5 dogs (delayed bypass group) using an operating microscope. The other 11 dogs without MA/MCA anastomosis were used as controls.

A common carotid angiogram of control animals was done 2 to 5 weeks after the occlusion, and a selective external carotid angiogram of animals with an anastomosis was done 2 weeks after making an MA/MCA anastomosis. When the animals were killed, transcarotid perfusion was carried out, and the brains examined histologically.

Eight of the 11 control animals showed mild to severe neurological defects, the other 3 died. In contrast, animals with patent bypass grafts, made soon after the MCA occlusion, showed no neurological defects.

Examination of the brains of control dogs showed that permanent occlusion caused medium to large infarcts in the territory supplied by the occluded MCA. Of the 8 dogs in the prompt bypass group, only 1 had an occluded bypass, and among the 7 dogs with a patent prompt bypass, 1 had no infarct and 6 had small infarcts detected microscopically. In the group with a patent delayed bypass, the clinical features were similar to those of the controls, but on postmortem examination the infarcts were found to be smaller than those in control animals. No hemorrhagic infarcts were found in either the prompt or delayed bypass group.

Results suggest that re-establishment of blood flow by construction of an extracranial-intracranial bypass, particularly if done soon after MCA occlusion, may be valuable for restoring neurological functions without causing appreciable pathological damage to the brain.

SINCE the development of techniques for microvascular surgery, extracranial-intracranial bypasses have been made as treatment for occlusive cerebrovascular disease. Theoretically, neurological defects should be reduced if the blood flow is restored by proper treatment after occlusion of a major cerebral artery. It has been reported that even when blood flow is restored soon after an occlusion, severe complications, such as brain edema and hemorrhagic infarcts, may develop.

One of the most important factors in surgical revascularization in occlusive cerebrovascular diseases is the length of time between the occlusion and surgery. This paper reports on the effects of an extracranial-intracranial bypass in dogs in the acute and chronic stages after MCA occlusion. Benefits and hazards are discussed.

Materials and Methods

Twenty-four mongrel dogs weighing 10 to 15 kg were anesthetized by intramuscular injection 5-10 mg/kg of ketamine. Tracheal intubation was performed and respiration was adjusted to the control level. A Y-shaped skin incision was made in the left temporoparietal region. The zygoma and choroid process were removed, the deep subtemporal muscle was resected and a small burr hole made in the temporal skull. The dura was opened and the middle cerebral artery (MCA) was ligated at its origin with 7-0 silk suture under microscopic control. End-to-side anastomosis of the maxillary artery (MA) and a branch of the MCA on the occluded side was made 4 hours later in 8 dogs (prompt bypass group), and 3 weeks later in 5 dogs (delayed bypass group) using an operating microscope. The other 11 dogs without MA/MCA anastomosis were used as controls.

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All the dogs were examined every day after MCA occlusion and graded as follows:

**Grade 0.** Neurologically intact.

**Grade 1.** Mild hemiparesis with ability to stand without assistance.

**Grade 2.** Moderate hemiparesis with ability to stand with assistance.

**Grade 3.** Hemiplegia with inability to stand even with assistance.

**Grade 4.** Death.

Angiography was carried out as follows: In the control group a left common carotid angiography was performed using 60% Conray (4 ml). In animals with a shunt, selective external carotid angiography was carried out 2 weeks after a bypass.

For histological examination, the dogs were killed by endocardial injection of KCl (20 ml). The brain was perfused with 10% formalin, removed and fixed in 10% formalin solution for 2 weeks. Then the brain was cut into coronal slices of 5 mm thickness, and the slices were embedded in paraffin, sectioned at 8 to 10 μ thickness and stained with hematoxylin-eosin, Klüver-Barrera and Elastica-Van Gieson stains.

The extent of infarct was graded as follows:

**Grade 0.** No infarct detectable.

**Grade 1.** Minute foci of infarction detected microscopically.

**Grade 2.** Infarcts of up to 7 mm diameter, usually confined to the basal ganglia and adjacent regions.

**Grade 3.** Infarcts of 7 mm to 15 mm diameter, usually involving the white matter near the outer corner of the lateral ventricle.

**Grade 4.** Large infarcts involving the whole territory of the MCA.

**Results**

Among the 11 control dogs without a bypass, 3 died on days 2, 3 and 5, respectively, after MCA occlusion, and the other 8 showed persistent moderate to severe neurological defects.

In the group of 8 dogs with a prompt bypass, only 1 with an occlusion of the anastomosis after MCA occlusion showed severe neurological defects. The other 7 with a patent bypass showed no neurological defects. Thus, animals with a patent bypass remained in better neurological condition than those with no bypass (fig. 1).

The clinical features of the group of dogs with delayed bypass were nearly the same as those in the control group. These animals showed no significant neurological improvement after construction of the anastomosis.

The common carotid angiogram in the control group showed no filling of the MCA. However, angiograms showed patent anastomoses in 7 of 8 dogs (88%) in the prompt bypass group, and in 4 of 5 dogs (80%) in the delayed bypass group. In these dogs with a patent anastomosis, the angiograms demonstrated good filling of all the MCA territory via the new shunt.

On histological examination, hemorrhagic lesions were found only in the brains of the 3 control dogs which died on days 2, 3 and 5, respectively, after the occlusion. No hemorrhagic lesions were found in the brains of any animals in the other 2 groups. The 3 control dogs which died showed moderate brain edema with a midline shift toward the contralateral side. In one dog with a prompt bypass no infarct was detectable. The brains of 20 dogs showed various degrees of anemic infarcts (table).

In the control group, large infarcts involving the entire territory supplied by the MCA (Grade 4) were found in 3 of 8 dogs. In Grade 4 lesions the cerebral parenchyma was markedly degenerated and its structural components were hardly distinguishable (fig. 2). The other 5 control dogs had Grade 3 or 2 infarcts in some of the MCA territory, and especially in the white matter near the outer corner of the lateral ventricle and part of the internal capsule (fig. 3).

In contrast, in the prompt bypass group, the brains were normal in size and showed neither edema nor atrophy. No destruction of parenchyma or loss of structure was seen in coronal sections. On histological examinations, no infarcts were found in 1 dog (Grade 0). Very small, spotty, infarcts near the basal ganglia (Grade 1) were found in the other 6 animals (fig. 4).
TABLE  Size of Anemic Infarcts in Control and Treated Dogs with MCA Occlusion

<table>
<thead>
<tr>
<th>Grade</th>
<th>Not treatment</th>
<th>Prompt MA-MCA anastomosis</th>
<th>Delayed MA-MCA anastomosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

In the delayed bypass group, lesions were found in the same regions as those in the control group, but these lesions were only Grade 3 or 2, and, unlike in the controls, no Grade 4 lesions were found.

Discussion

After occlusion of a major cerebral artery, hemococontion, sludging, stasis and spasm may occur in areas of ischemia, and these complications increase the infarction. Harvey and Rasmussen found that the extent of infarction varied with the duration of MCA occlusion, and that permanent irreversible brain damage usually developed after MCA occlusion for about 50 minutes or more. Shintani studied the effect of the duration of MCA occlusion in squirrel monkeys, and concluded that hemorrhagic infarcts might develop even if reconstructive surgery was performed immediately after MCA occlusion. On the contrary, Crowell et al. reported from animal studies that surgical revascularization within a few hours after MCA occlusion resulted in significant restoration of neurological function, and that if blood flow was established within 4 hours after the occlusion, the development of hemorrhagic infarcts could be prevented.

In the present experiment, the clinical and neurohistological features of the dogs with a patent prompt bypass differed distinctly from those of the control group. All the control dogs showed moderate or severe neurological defects and histologically many of them had Grade 3 or 4 lesions. However, none of the dogs with a patent prompt bypass showed neurological defects and brains appeared almost normal at post-mortem. Thus the blood supply through the new shunt had a favorable effect on the ischemic area and prevented developments of functional and structural defects.

In clinical practice it is usually not possible to carry out the shunt operation within a few hours after occlusion of the major cerebral artery; the operation usually is done a week or more after appearance of clinical symptoms. In such cases revascularization...
might be effective if the nerve cells are not irreversibly damaged. In the present study, the infarcts in the delayed bypass group were more extensive than those in the prompt bypass group, indicating that the lesions became more extensive during the 3-week period before the bypass was made.

The extent and grade of infarcts in the dogs with a patent delayed bypass were, in general, less than those found in the control dogs, suggesting that physiologically paralyzed areas that had not yet become necrotic recovered with re-establishment of the blood flow, even though construction of the shunt was delayed.

There are many clinical reports that neurological defects due to occlusive cerebrovascular diseases were improved by surgical restoration of the blood flow, especially when revascularization was achieved within a few hours after onset of symptoms. On the other hand, there are also reports that hemorrhagic infarcts were caused by immediate operations such as thrombendarterectomy. In the present experiment, hemorrhagic lesions were found in 3 control dogs which died on days 2, 3 and 5, respectively, after the occlusion. The risk of hemorrhagic infarcts may be latent in the early stage after resumption of the blood flow. Other factors may also affect development of hemorrhagic infarcts. Infarcts often develop in patients with restored blood flow after endarterectomy for occlusive disease of the extracranial internal carotid artery. Thus, although it is said that bypass formation rarely causes hemorrhagic infarcts, the change of hemodynamics after this surgical treatment, i.e., "normograde" or "retrograde" flow, also seems to be a contributory factor in development of hemorrhagic infarcts.

In our experiments, no hemorrhagic infarcts were recognized in either the prompt or delayed bypass group. From electronmicroscopic studies on the cerebral blood vessels after occlusion, Garcia et al. reported that necrosis of endothelial cells was not detectable for 12 hours after occlusion, but that significant structural abnormalities began to develop at that time. This change in the endothelial cells may be one of the factors that causes hemorrhagic infarcts. Olsson et al. reported that regardless of the size of infarcts restoration of vascular permeability occurs 3 weeks or more after MCA occlusion. If the blood flow is restored by surgical revascularization when damage of the vascular wall is still slight, or when the wall has been repaired, it is believed that the vessel wall may be able to sustain the arterial pressure. Anatomical and physiological control mechanisms tend to compensate for circulatory and metabolic disturbance in ischemic areas resulting from occlusion of the major cerebral artery. The collateral circulation is thus important in preventing irreversible changes of the nerve cells. To prevent such changes in the ischemic areas, it is essential to re-establish blood flow early after the occlusion.

Too few dogs were used in this study to draw definite conclusions, but the results obtained strongly suggest that restoration of blood flow by extracranial-intracranial bypass using end-to-side anastomosis, especially when the bypass is made soon after occlusion, may result in significant improvement of neurological function without appreciable pathological damage to the brain and may reduce the incidence of hemorrhagic infarcts.

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