Experimental microsurgical embolectomy after middle cerebral artery embolization in the dog

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The effects of microsurgical embolectomy were investigated clinicopathophysiologically in 60 dogs after occlusion of the middle cerebral artery (MCA) trunk with a silicone cylinder embolus. One group of animals served as a control (non-embolectomized group), and in the other two groups the embolus was removed 3 or 6 hours after occlusion (3-hour or 6-hour embolectomy group). In the non-embolectomized animals, major neurological deficits with deep cerebral infarction were observed. Regional cerebral blood flow (CBF) in the basal ganglia decreased most prominently. Sensory evoked potentials also declined to about 50% of the control level 3 hours after embolization. In the 3-hour embolectomy group, mild neurological deficits with minimal infarctions were found. One hour after embolectomy, CBF was restored to the original level in all regions, and the sensory evoked potentials surpassed the control level. In the 6-hour embolectomy group, most animals exhibited major neurological deficits and severe brain swelling with hemorrhagic infarction. This study suggests that early microsurgical embolectomy of the MCA trunk restores blood flow in the perforating arteries and prevents deep cerebral infarction.

KEY WORDS • embolization • embolectomy • evoked potentials • cerebral blood flow • cerebral infarction • middle cerebral artery occlusion

RESTORATION of cerebral blood flow (CBF) has been considered a simple and rational procedure for relieving the brain from irreversible changes in the acute stage of ischemia. Since Welch reported his success with thromboendarterectomy of the intracranial arteries in man, effective restoration of CBF has been described by several authors. There has, however, been controversy as to whether restoration of flow is effective in the acute stage, because restoration has resulted in various complications and aggravation of the patients' condition in many instances. In order to determine the effects of early surgical restoration of circulation to the ischemic human brain, it is desirable to prepare experimental models that resemble the clinical situation as closely as possible.

We induced regional cerebral ischemia by silicone cylinder embolization of the middle cerebral artery (MCA) trunk in dogs, since this model is one that closely resembles deep cerebral infarction in man. The CBF was restored by microsurgical embolectomy in two groups of dogs at 3 or 6 hours after MCA embolization, and the effect of surgery was evaluated clinicopathologically up to 1 week after surgery. Furthermore, regional CBF and sensory evoked potentials were measured to investigate the effects of embolectomy.

Materials and Methods

Sixty adult mongrel dogs, weighing 8 to 20 kg, were anesthetized with sodium pentobarbital (25 to 30 mg/kg intravenously), and respiration was controlled mechanically after endotracheal intubation. Systemic arterial blood pressure and arterial blood gases were measured during the experimental procedures.

Embolization and Microsurgical Embolectomy

A silicone cylinder, 1.1 mm in diameter and 8 mm in length, was injected into the right cervical internal carotid artery to occlude the MCA trunk. Silicone cylinders with a 4-0 thread embedded in them so as to protrude about 1 mm from the end, were used to facilitate the embolectomy. The animals undergoing embolization were separated into three groups. One group of 35 dogs served as the control series, in which
the embolus was not removed (non-embolectomized group); in the other two groups the embolus was removed, in 15 dogs at 3 hours and in 10 dogs at 6 hours after embolization (3-hour or 6-hour embolectomy group). To accomplish the embolectomy 3 or 6 hours after embolization, surgical procedures were commenced about 90 minutes in advance of embolectomy.

A right coronal scalp incision was made and the temporal muscle was dissected down to the zygomatic arch. A right temporal craniectomy was carried out to visualize the silicone cylinder that had been introduced into the MCA trunk (Fig. 1a). The arachnoid membrane was carefully detached with the aid of an operating microscope, and Scoville microclips were applied to the main branches of the MCA (Fig. 1b). An incision 2 to 3 mm in length was made in the MCA trunk so that the protruding end of the thread could be grasped (Fig. 1c). As soon as the cylinder was gently extracted, the MCA trunk was clipped as close to the arterial incision as possible (Fig. 1d). The incision was closed with a few 10-0 nylon sutures, after which the temporary clips were removed and circulation was restored (Fig. 1e). Careful inspection was carried out to ascertain that there was no hemorrhage or marked stenosis (Fig. 1f).

In the 6-hour embolectomy group, 20% glycerol was administered intravenously during surgery. These operative procedures were performed under sterile conditions, and antibiotics were administered intravenously.

Clinicopathological Features

The neurological deficits were estimated on the basis of a modification of the neurological evaluation scale described by Smith, et al., as follows:

0 = no neurological deficits
1 = mild neurological deficits, such as forced circling, hemianopsia, and left forelimb weakness
2 = can stand without support, but walks poorly with evidence of hemiplegia
3 = cannot stand without support
4 = no spontaneous activity or died.

The neurological score was recorded daily for up to 1 week, after which the animals were sacrificed.
Experimental Embolectomy

After the dogs were sacrificed or died, the brain was removed, studied grossly, and fixed in 10% formalin solution. Coronal sections were made 5 mm thick, and the infarct volume was calculated by the averaged-end area method from photographs with a planimeter. Representative areas of brain tissue were fixed in paraffin, and blocks were sectioned for hematoxylin and eosin staining.

Regional Cerebral Blood Flow

Regional cerebral blood flow (rCBF) was measured by the hydrogen clearance method at the cortex of the anterior and posterior Sylvian gyrus and the basal ganglia in the non-embolectomized and 3-hour embolectomy groups. After the dogs were prepared for embolization, the head was fixed in a stereotaxic apparatus. Right temporal craniectomy was performed to attach hydrogen electrodes (platinum wire 300 μm in diameter insulated with Teflon up to 1 mm of the tip) at the anterior and posterior Sylvian gyrus approximately 1 cm from the trifurcation of the MCA. Another hydrogen electrode was introduced into the putamen using the technique of Lim, et al., to measure rCBF at the basal ganglia. Large Ag/AgCl electrodes were placed subcutaneously in the scalp to serve as reference electrodes. All electrodes were allowed to stabilize for at least 30 minutes after placement in the tissue, and clearance curves were recorded after inhalation of 10% hydrogen gas for 1 to 2 minutes. Blood flow was calculated by the initial-slope method.

Sensory Evoked Potentials

Sensory evoked potentials (SEP) were recorded on the occluded side in response to contralateral median nerve stimulation in the non-embolectomized and the 3-hour embolectomy groups. A bipolar stimulus electrode was placed on the left median nerve, and stimulation (2 to 3 V, 1 msec, 1 Hz) was applied to the nerve with an electronic stimulator. The cortical electrode was positioned on the dura at the sensory cortex area with a reference electrode on the ear. Signals from the cortical electrode were amplified and averaged on-line by computer with a 100-msec sweep time of 100 responses produced by median nerve stimulation. The averaged peak-to-peak amplitude of the primary response was expressed as a percentage of the control amplitude recorded before MCA embolization.

Following control measurements of rCBF and SEP, the MCA trunk was occluded and these variables were measured every hour for 6 hours. In the 3-hour embolectomy group, rCBF and SEP could not be measured at the 2nd and 3rd hour because the cortical and hydrogen electrodes were removed during preparation for embolectomy.

Neurological Scoring

The 60 animals were separated into the three groups described above, namely, 35 non-embolectomized animals, 15 animals with 3-hour embolectomy, and 10 animals with 6-hour embolectomy. Twenty-five non-embolectomized, eight 3-hour embolectomized, and 10 6-hour embolectomized animals were prepared for recording the daily neurological score for 1 week. These animals, except for 10 non-embolectomized animals, were sacrificed on the 7th day after embolization or embolectomy and examined pathologically. In the 10 non-embolectomized animals, the daily neurological score was recorded for a total of more than 2 weeks. In this study, we analyzed clinicopathological changes within 1 week after embolization or embolectomy. The rCBF at the basal ganglia and anterior Sylvian gyrus was measured simultaneously in 10 non-embolectomized and seven 3-hour embolectomized animals which were sacrificed immediately after the measurements. In another eight non-embolectomized and six 3-hour embolectomized animals, the rCBF at the posterior Sylvian gyrus and the SEP were measured simultaneously, and clinicopathological changes were observed for 1 week. The SEP only were measured in another three dogs, for a total of 11 non-embolectomized animals, and one additional dog, for a total of seven 3-hour embolectomized animals. These dogs were also kept alive for clinicopathological observation.

Statistical significance of the results was determined using Student’s t-test, and p < 0.05 was considered significant.

Results

When all animals were observed for 1 week, the total number of days of observation would be 175, 56, and 70 days in 25 non-embolectomized animals, eight 3-hour embolectomized animals, and 10 6-hour embolectomized animals, respectively. But, since some animals died during this time, the actual number of days of observation was reduced to 161, 52, and 62 days in the non-embolectomized animals, 3-hour embolectomized animals, and 6-hour embolectomized animals, respectively. All these daily neurological scores were analyzed by counting the total number of days with the same score. These results are shown in Fig. 2A. Most of the non-embolectomized animals exhibited major neurological deficits, such as hemiplegia, forced circling, and hemianopsia. Score 3 was observed in 18 of the 25 non-embolectomized animals, for a total of 66 days. In 16 animals, Score 2 was noted for a total of 48 days. And in six of the 25 animals, Score 4 was recorded for a total of 18 days, but four of the six had died by 5 days after embolization. The averaged neurological score was 2.6 ± 0.2 (mean ± SE) during this period (Fig. 2B).

One of the eight 3-hour embolectomized animals died on the 3rd day, and two animals exhibited hemiparesis. Thus, in one of the eight animals, Score 4 was
observed for a total of 3 days, in three animals Score 2 was noted for a total of 10 days, and in four animals Score 1 was recorded for a total of 28 days. The distribution of neurological score in the 3-hour embolectomy group definitely differed from that of the non-embolectomized group (Fig. 2A). The averaged neurological score in the 3-hour embolectomy group was 1.1 ± 0.4, which was significantly different from that in the non-embolectomized group.

Two of the 10 6-hour embolectomized animals died by the 3rd day, and three others exhibited major neurological deficits. The remaining five animals also displayed hemiparesis, but regained their ability to walk after the 2nd day. Daily neurological scores showed that Score 4 was observed for 6 days in two animals. Three animals had Score 3 for a total of 21 days, five animals had Score 1 for 25 days, and three animals had Score 0 for 10 days. This distribution was similar to that in the non-embolectomized group (Fig. 2A). The averaged score in the 6-hour embolectomy group was 2.1 ± 0.4, which did not differ significantly from that in the non-embolectomized group (Fig. 2B).

Pathological Findings

The brains from 13 of the 15 non-embolectomized animals that died within 1 week or were sacrificed on the 7th day after embolization showed marked swelling, and the cut surfaces exhibited prominent shift of midline structures and distinct lesions with softening and discoloration in the deep cerebral area. The other two animals that died on the 3rd day presented prominent brain swelling, but we could not find macroscopic lesions on the cut surfaces of these brains. Most of the lesions in the 13 animals were ischemic infarction, but four animals revealed hemorrhagic infarction. The average infarct volume in these 13 non-embolectomized animals was 4.1 ± 0.4 (mean ± SE) cu cm (Fig. 2B). Microscopically, destructive lesions with necrosis and inflammatory cell infiltration were demonstrated in all cases.

In the 3-hour embolectomy group, brain swelling and shift of midline structures were observed in all eight animals. A hemorrhagic infarction of about 4 cu cm was seen at the temporal lobe in one, and small hemorrhagic lesions of approximately 1 cu cm were found in the caudate nucleus and claustrum in two animals. The mean infarct volume in this group was 1.1 ± 0.5 cu cm, which was significantly different from that in the non-embolectomized group (Fig. 2B).

In the 6-hour embolectomy group, all animals showed prominent brain swelling with bulging of the hemisphere at the craniectomy site and shift of midline structures (Fig. 3). While three out of 10 animals exhibited ischemic infarction, the other six animals presented hemorrhagic infarction or intracerebral hematoma. The mean infarct volume was 2.9 ± 0.5 cu cm in this group, which did not differ from that in the non-embolectomized group (Fig. 2B).

Regional Cerebral Blood Flow

The changes in rCBF in the non-embolectomized and the 3-hour embolectomy groups are shown in Fig.
Experimental embolectomy

FIG. 3. A: Ventral surface of the brain 7 days after surgery in the 6-hour embolectomy group shows bulging at the site of craniectomy (arrow) and slight hemorrhage in the temporal lobe. B: Cut surface of the brain shown in A exhibits prominent brain swelling and hemorrhagic infarction.

4. The mean values of rCBF prior to embolization were 50 to 65 ml/100 gm/min, which did not differ significantly at the three regions in either group. One hour after embolization, rCBF decreased significantly at the three regions in the non-embolectomized group. In the 3-hour embolectomy group, rCBF decreased significantly to 24.7 ± 2.3, 34.1 ± 2.2, and 42.3 ± 3.7 ml/100 gm/min at the basal ganglia, and anterior and posterior Sylvian gyrus, respectively. The decrease in rCBF did not differ significantly between the non-embolectomized and the 3-hour embolectomy group at the corresponding regions. The most prominent reduction in rCBF was observed at the basal ganglia, where the decrease reached 40% to 50% of the control levels.

FIG. 4. The regional cerebral blood flow (rCBF) at the cortex of the anterior Sylvian gyrus (black circle) and posterior Sylvian gyrus (square), and basal ganglia (white circle) on the side with MCA occlusion in the non-embolectomized (A) and 3-hour embolectomy (B) groups. The rCBF at the three regions decreased significantly after embolization, but the decreased blood flow in all regions was restored to the preocclusion levels after embolectomy.
Sensory Evoked Potentials

Typical changes in SEP in the non-embolectomized and the 3-hour embolectomy groups are shown in Fig. 5A and B, respectively. In the non-embolectomized group, SEP declined progressively following the embolization of the MCA trunk, whereas in the 3-hour embolectomy group, the SEP which had dropped following embolization surpassed the preocclusional level after embolectomy.

Figure 5C shows mean relative changes in SEP in both the non-embolectomized and the 3-hour embolectomy groups. In the non-embolectomized group, the mean SEP in 11 animals decreased from the control value of 100% to 72.3 ± 8.2% (mean ± SE) at 1 hour after embolization. This reduction continued, and reached 53.0 ± 7.2% by the 3rd hour. In the 3-hour embolectomy group, the mean SEP in seven animals decreased significantly to 87.8 ± 4.0% at 1 hour after embolization. One hour after embolectomy, SEP increased to 115.4 ± 10.1% (a level not statistically significant in comparison to the control level), and continued to increase during the 3 hours after embolectomy (Fig. 5C). The mean SEP in the 3-hour embolectomy group differed significantly from those in the non-embolectomized group at the corresponding times after embolectomy.

Arterial Blood Pressure and Gas Analysis

The mean arterial blood pressure was maintained, ranging from 90 to 130 mm Hg during surgery, and increased gradually about 10% during the period of 6 hours after embolization. Arterial blood gas analyses showed normoxia and normocapnia during the experiment.

Discussion

Many experimental studies have been carried out to investigate the effects of restoration of CBF by means of intracranial-extracranial bypass, removal of an occluding clip, or embolectomy in various models. Experimental microsurgical embolectomy, however, seems to be one of the most valuable models, because it mimics the surgical procedures for recanalization in humans. Further, embolization with a silicone cylinder in the MCA trunk has been known to produce a distinct deep cerebral infarction resulting from direct occlusion of the orifices of the perforating arteries.

In our study, moderate retrograde bleeding from the perforating arteries was observed (Fig. 1d), which suggests that the perforating arteries are not terminal arteries and that restoration of flow to these arteries is possible within 6 hours after embolization. Furthermore, this bleeding makes the surgical procedures so...
The perforating arteries. indicates the possibility of successful recanalization in of rCBF in the 3-hour embolectomy group, which present study, we were able to demonstrate recovery rCBF following embolectomy for occlusion of the clipping models; however, few reports describing segmental MCA trunk have been published. In the superficial temporal artery (STA)- MCA anastomosis an increase in rCBF to the control level following clipping, but is increased to 200% following recanali-

The only study on experimental embolec-
tomy in which effective restoration was achieved 2 hours after embolization was made by Dujovny, et al. From these clinicopathological studies, the critical time is considered to be 3 to 6 hours after MCA occlusion.

In addition to the duration of ischemia, the degree of the ischemia and restored rCBF are important factors in obtaining effective restoration of CBF. The blood flow required for maintaining cerebral function has been reported to be 16 to 20 ml/100 gm/min, based on clinical and experimental studies. In our non-embolized group, an rCBF of 21.5 ± 2.7 ml/100 gm/min at the basal ganglia, where infarction has been observed most frequently, is considered to be a critical level. It should be noted, however, that rCBF following restoration has been measured in many stroke models by various methods. Sundt, et al, using the Krypton-85 washout method, have reported that the rCBF is reduced to 20% to 50% of the control level in the squirrel monkey by MCA clipping, but is increased to 200% following recanalization 2 hours later. Fein and Molinari also described an increase in rCBF to the control level following superficial temporal artery (STA)- MCA anastomosis for MCA clipping in dogs using the Xenon-133 washout method. These studies were performed in MCA clipping models; however, few reports describing rCBF following embolectomy for occlusion of the segmental MCA trunk have been published. In the present study, we were able to demonstrate recovery of rCBF in the 3-hour embolectomy group, which indicates the possibility of successful recanalization in the perforating arteries.

Restored blood flow, however, has not always been associated with functional recovery, as transformation of brain swelling and hemorrhage into ischemic lesions has been frequently noted. Therefore, CBF and cerebral function should be measured simultaneously. As indices of cerebral function, evoked potentials have often been applied to evaluate clinical and experimental brain dysfunction. Ito, et al, have published an interesting report to determine the indications for operative restoration of CBF in complete stroke patients, in which the response of rCBF and evoked potentials are monitored under induced hypotension. Branston, et al, have recorded rCBF and SEP simultaneously in baboons with MCA occlusion, and suggested that SEP start to decline at an rCBF of 16 ml/100 gm/min and cease completely at 12 ml/100 gm/min in the cortex. Furthermore, when CBF is restored within 30 to 60 minutes, rCBF and SEP recover (showing an exponential relationship). In the 3-hour embolectomy group, we observed that rCBF increased to the control level and SEP surpassed the preocclusion level after embolectomy, in contrast to the progressive decrease in SEP in the non-embolotomized group. These changes in rCBF and SEP in the non-embolotomized and the 3-hour embolectomy groups suggest that these indices are closely related to clinicopathological results caused by MCA trunk occlusion.

Conservative therapy has also been attempted in order to obtain effective restoration. Many types of therapy, such as increased perfusion pressure, hemo-
dilution for improvement of microcirculation, and several drugs have been tried. Recently, attention has been focused on barbiturates. Using our embolization model, Yamamoto, et al, studied the effects of barbiturate therapy from the viewpoint of cerebral energy metabolism, and demonstrated favorable results. Laha, et al, have administered dimethyl sulfoxide and methylprednisolone and achieved effective experimental embolotomy within 6 hours after occlusion. There are many problems involved in the application of such conservative therapeutic measures. However, the development of such means of therapy is essential for the effective surgical restoration of CBF in the acute stage.

References

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