Cerebral Infarction in Rats Using Homologous Blood Emboli: Development of a New Experimental Model

DAISEI KANEKO, M.D., NORIO NAKAMURA, M.D., AND TAKEKI OGAWA, M.D.

SUMMARY A reproducible model of thromboembolism in the rat was developed and the temporal relationship between hydrogen clearance, regional cerebral blood flow (rCBF) and power spectral-analyzed electroencephalographic (EEG) activity explored for up to four hours postinsult. Sixteen rats were subjected to right internal carotid artery homologous blood embolization after electrocautery of the pterygopalatine artery. Four rats were subjected to sham operation. Cerebral angiography before and for up to four hours postinsult was used to verify the distal migration and fragmentation of the emboli. Preembolic mean rCBF was 62 ± 9 ml • 100g⁻¹ • min⁻¹ and 65 ± 12 ml • 100g⁻¹ • min⁻¹ in the embolized and contralateral sides, respectively. Based upon the distribution of the emboli at sacrifice, the experimental group of 12 rats fell into three subgroups: (1) unilateral proximal embolism, n = 8; (2) unilateral peripheral embolism, n = 3; and (3) bilateral proximal embolism, n = 1. In unilateral proximal embolism the mean rCBF in the embolized hemisphere fell significantly 30 min postembolism. It returned progressively towards preembolic values as the embolic clots migrated distally and fragmented. Despite the restoration of rCBF, recovery of EEG activity appeared to be delayed. Our results did not show luxury perfusion after embolic insults. The time course for the reopening of the embolized artery and the delay in recovery of neuronal function (i.e., EEG activity) relative to the restoration of rCBF are discussed.

CEREBRAL EMBOLISM resulting in cerebral ischemia and infarction is a major clinical problem which has stimulated the development of various experimental models. Of the models used, the rat has the advantage that, compared to other species such as the gerbil, cat and dog, its cerebral circulation more closely resembles that of man. It is also inexpensive. Cerebral embolism with homologous blood clots may not be as convenient as foreign bodies, but should better simulate the clinical situation.

In the rat, injection of emboli into the common carotid artery results in intracranial, but also extracranial embolization and variable degrees of cerebral embolization. This is likely due to the pterygopalatine artery which receives an ample blood supply as a major branch of the internal carotid artery (figure 1). Thus, in our experimental model, the pterygopalatine artery is permanently occluded before homologous emboli are injected. The aims in this study were: (1) to develop a reproducible model of cerebral thromboembolism in the rat; (2) to explore the temporal correlation between regional cerebral blood flow (rCBF) and electroencephalographic (EEG) activity using power spectral analysis during cerebral infarction; and (3) to investigate the natural history and fate of the emboli after lodging in the cerebrovasculature and to compare these with clinical observations made in stroke patients.

Methods

Preparation of Blood Clot and Technique for Embolus Formation

We used a modification of the methods described by Kudo et al. Briefly, 36 hours before the experiment, sixteen female Wistar rats weighing from 240 to 300 grams were anesthetized with two percent halothane/60% O₂/40% N₂. Fifty μl of blood was obtained by cardiac puncture and stored at room temperature for clot formation. The rats were allowed to recover from anesthesia. The blood was diluted with 0.3 ml of saline and the clot was fragmented through a 27 gauge needle. The size of the clot fragments averaged between 100 and 200 μm, as measured by micrometer.

Experimental Procedures

Thirty-six hours later, the rats were reanesthetized with sodium pentobarbital, 30 mg/kg (Nembutal, Abbott Laboratories) intraperitoneally (IP), after intramuscular (IM) administration of atropine sulfate 0.1 ml (Tanabe, Inc.). Polyethylene catheters were inserted into the trachea, and the rats were mechanically ventilated (rodent ventilator, Harvard Apparatus) on 60% O₂/40% N₂. Femoral artery and vein catheters (PE-50, Clay Adams, Inc.) were inserted and the rats were immobilized with intravenous (IV) pancuronium bromide, 0.1 mg, (Mibloc, Organon, Inc.) hourly. A rectal thermistor (Nihonkoden Kogyo, Inc.) was inserted and temperature maintained at 37°C with an electric lamp. Arterial blood pressure was continuously recorded on a polygraph (RM-6000, Nihonkoden, Inc.) via a pressure transducer (Statham P23ID, Gould, Inc.) and mean values controlled between 120 and 80 mm Hg.

Catheterization technique: Under an operating microscope, the right wing of the hyoid bone was removed. The right glossohypoglossal nerve was followed to the skull base (point A in fig. 1) where the pterygopalatine artery was identified and electrocauterized with a bipolar coagulator. The bifurcation of the right common carotid and external carotid arteries was exposed (B-C in fig. 1). A temporary clip (Zen clip, Ohwa Tsusho, Co.) was applied to the external carotid artery just above its origin (point B in fig. 1).
The artery was cannulated retrograde (C to B in fig. 1) with the catheter tip still in the external carotid artery, but at the entrance to the internal carotid artery. Thus, cerebral embolization could be done via the internal carotid artery without obstructing blood flow before or after the insult.

The skin overlying the calvarium was removed and the muscle scraped away from the dorsal and lateral aspects of the skull. The rat’s head was fixed in a stereotaxic apparatus (Takahashi, Inc.). Cranietomies (3 mm diam) were made bilaterally one mm posterior and five mm lateral to the bregma. Teflon-coated platinum wires with bared tips of 0.5 mm length and 0.2 mm diameter were stereotaxically inserted into the parietal cortex to a depth of 0.5 mm. A reference electrode of Ag/AgCl for rCBF was placed on the dorsal aspect of the neck. A platinum reference EEG electrode was inserted subcutaneously over the midfrontal region. The cranietomies and skin defect overlying the calvarium were sealed with agar-agar in 0.9% NaCl (fig. 2).

Approximately 1.5 hours were required for the preparation of the rat. Thereafter, a one hour stabilization period was allowed, while arterial blood samples (0.4 ml) were obtained to verify normal arterial blood gas values on a trielectrode blood gas unit (Corning model, 175, Fisher Scientific, Inc.); PaO₂, > 100 mm Hg; PaCO₂, 35-45 mm Hg; pHa, 7.3-7.4; and base excess ± 5 mEq/l was corrected with 7% sodium bicarbonate.

The embolic insult was induced in 12 of 16 rats by the injection of 0.4 ml of clot suspension into the internal carotid artery over one to two min. Four rats (sham operated) received carotid injections of 0.4 ml of physiologic saline. Two-tailed student’s t-tests for unpaired comparisons were used for statistical analysis. P values equal to or less than 0.05 were considered statistically significant.

EEG and rCBF

EEG activity from the platinum electrodes in the parietal cortex was recorded on a polygraph (RM-6000, Nihonkoden, Inc.) and simultaneously stored on magnetic tape for power spectral analysis. After recording the EEG, the electrodes were connected to the rCBF measuring system and the rCBF determined at each period in the experiment. EEG recordings and rCBF measurements were made before, and 30, 60, 120, and 240 min after embolization. Immediately after embolization, the EEG was continuously recorded for 10 min and analyzed at 5 and 10 min postembolism. Regional cerebral blood flow was determined by 5% H₂ gas inhalation for three to five minutes followed by desaturation. Regional CBF was calculated using the two min initial slope index determined by the least squares method.

Power spectral analysis of the initial EEG was done with a medical computer (Signal Processor Model 7T08, Sanei Sokki, Inc.), using the Fast Fourier Transform. Twenty second samples were digitized and frequency bands were determined in the following ranges: Delta, 1.0–3.5 Hz; Theta, 3.5–7.5 Hz; Alpha 1, 7.5–10 Hz; Alpha 2, 10–13 Hz; Beta 1, 13–18 Hz; Beta 2, 18–30 Hz. The percent power of each frequency band was determined.

Angiographic Examination

Angiograms were done in four rats immediately before introduction of the emboli, and at 5, 60 and 240 min postembolism. Arteriographic studies consisted of
a single axial view. Meglumine isothalamate, 60% (0.1 ml) was injected as the contrast agent into the common carotid artery.

### Histopathological Examination

After all measurements were completed at four h postembolism, 0.5 ml of 2% Evans blue dye solution was injected IV. Thirty min later, a cannula was introduced into the ascending aorta via the left ventricle and the brain was perfused fixed with physiological saline followed by four percent formalin. The brain was inspected under an operating microscope to determine the location of the embolized clots. After immersion in 4% formalin for a week, coronal sections were made and inspected for leakage of dye and shift of midline structures. Histological studies were done with serial sections around the electrodes with hematoxylin-eosin and Kluver-Barrera (Nissl-myelin) stains.

### Results

Arterial blood gases, pH and body temperature were similar in sham-operated (table 1) and experimental (table 2) groups, but mean arterial pressure (MAP) progressively fell. In sham-operated rats, MAP was significantly lower four hours after sham embolism, whereas in the experimental group MAP had already significantly declined below preembolic levels at 2 hours. In the experimental group, one rat was sacrificed at 180 min and two rats at 240 min postembolism because MAP fell below 60 mm Hg.

#### Location of the Emboli at Sacrifice

Based on the distribution of the embolic clots at sacrifice, the experimental group of 12 rats fell into the following 3 subgroups: (1) Unilateral proximal embolism (8/12 rats) — clots located within the proximal trunk of the middle cerebral artery (MCA) of the embolized side, but not beyond the cortical ascending portion of the MCA with variable occlusion of the anterior cerebral (ACA) and posterior cerebral (PCA) arteries (fig. 3); (2) unilateral peripheral embolism (3/12 rats) — no emboli within the major branch of MCA, but with very small clots in the peripheral territory of MCA; and (3) bilateral proximal embolism (1/12) — emboli in the proximal trunk of MCA. However, two rats in unilateral proximal embolism and one in peripheral embolism had small fragmented emboli in the peripheral area of the contralateral hemisphere.

#### rCBF and EEG

Mean rCBF prior to embolism in the sham-operated group was 55 ± 3 ml · 100g⁻¹ · min⁻¹ on the sham-operated side. Prior to embolism, all the rats had a normal EEG with no interictal discharges. rCBF was significantly reduced at 240 min postembolism in all the rats, but no abnormal EEG changes were observed.

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### Table 1: Physiological Variables in Experimental Group (n = 12)

<table>
<thead>
<tr>
<th>Time</th>
<th>PaO₂ mmHg</th>
<th>PaCO₂ mmHg</th>
<th>pHa</th>
<th>BE mEq/L</th>
<th>MAP mmHg</th>
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<td>263</td>
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*p < 0.05 compared to pre-embolism value.

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### Table 2: Physiological Variables in Sham Operated Group (n = 4)

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<th>pHa</th>
<th>BE mEq/L</th>
<th>MAP mmHg</th>
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*p < 0.05 compared to pre-embolism value.
Unilateral proximal embolism. embodied (n=8)

Unilateral peripheral embolism or clotlysis. embolized (n=3)

Bilateral proximal embolism. (n=1)

FIGURE 4A. The time course of mean rCBF values in experimental group (n=12). Pre-embolism, mean rCBF value was 62 ± 9 ml·100g⁻¹·min⁻¹ in the embolized and 65 ± 12 ml·100g⁻¹·min⁻¹ in the contralateral side. Embolic insult was induced by injecting 0.4 ml saline with 100 to 200 μm of clot particles obtained from 0.05 ml whole blood. Post-embolism, mean rCBF values of the embolized side were significantly lower (p < 0.05) than the contralateral side throughout the whole period of study.

FIGURE 3. Right lateral (A) and basal (B) view of the brain of unilateral proximal embolism rat. The embolized clot is seen lodged in the proximal portion of MCA.

Unilateral proximal embolism: Preembolic rCBF in the embolized side was significantly lower than in the contralateral side (fig. 4A). In the sham-operated group, rCBF was unchanged.

Preembolic power spectra were similar in the sham-operated and the experimental groups. The percent power of the delta frequency band in the sham-operated group gradually decreased while the theta and alpha frequency bands increased. Thus, in the sham-operated rats, mean frequency progressively rose compared to preembolic values. In the experimental group, immediately after the embolic insult, the delta frequency band increased while the theta and alpha frequency bands and the mean EEG frequency decreased on the embolized side (fig. 4B). EEG depression occurred immediately after embolism with maximum depression at 10 min postembolism then slowly recovered.

Changes in both rCBF and EEG were analyzed in each of the experimental subgroups. Unilateral proximal embolism: Preembolic rCBF 64 ± 14 ml·100g⁻¹·min⁻¹ on the contralateral side (fig. 5A). Postembolism, mean rCBF on the embolized side was lower and ranged between 10 and 20 ml·100g⁻¹·min⁻¹ throughout. Contralaterally, a gradual decrease in mean rCBF appeared to occur, but was not significant. EEG power spectra showed significant differences between the embolized and nonembolized sides (fig. 5B). Changes in rCBF correlated with changes in EEG activity.

Unilateral peripheral embolism: Preembolic mean rCBF was 62 ± 10 ml·100g⁻¹·min⁻¹ on the embolized side and 66 ± 11 ml/100g/min on the contralateral side (fig. 6A). In the embolized side it showed a significant decrease at 30 min postembolism and progressively rose towards, but not higher than preembolic values. The EEG gradually recovered after the embolic insult.
embolization, but recovery of rCBF appeared disproportionate relative to recovery of EEG on the embolized side. The EEG remained depressed until 240 min postembolism in the delta and alpha frequency bands (fig. 6B). Thus, in this group, changes in the EEG activity did not correlate with changes in rCBF. On the contralateral side rCBF remained unchanged throughout the experiment despite a transient rise at 30 min postembolism.

Angiographic Examination

Preembolism, only the intracranial arteries were opacified due to the occlusion of the pterygopalatine artery (fig. 7A). Five min after embolization, the internal carotid artery was completely blocked (fig. 7B). An hour later, the emboli had migrated distally and the previously obstructed internal carotid artery was now visible even though the inner surface of the vessel was still irregular (fig. 7C). At four hours, a more distal migration was seen and the previously blocked middle cerebral artery was visualized (fig. 7D).

Histopathological Examination

Severe damage in the cerebral cortex, subcortical white matter and basal ganglia occurred in all rats with proximal embolism. Infarcts of variable sizes and degrees were observed along the electrodes in all of these animals. A midline shift was observed in three of eight rats. Evans blue leakage occurred within the cerebral cortex of one rat, and in the basal ganglia in six of 12 rats. Cortical and subcortical infarctions were usually of the pale or anemic type (fig. 8).

No cortical damage was observed around the electrodes in rats with peripheral embolism. In one rat, however, bilateral anemic infarctions occurred in the basal ganglia.

Discussion

Two technical aspects of our studies that may have influenced our observations deserve comment before discussion of our findings. First, it should be emphasized that in our studies, the rats were mechanically ventilated with 60% O₂ resulting in PaO₂ of over 200 torr. Although this should have a minimal effect on the O₂ carrying capacity of the blood, it may have a beneficial effect on the severity of the ischemic changes observed in the brain and systemic circulation. Indeed, in a few preliminary studies done on room air, arterial pressure fell more rapidly postinsult than observed in this study. Thus, by both maintaining better cerebral perfusion pressure and arterial oxygenation, our use of 60% O₂ may have attenuated the changes that would have occurred on room air.

Second, because of the potential for error in our rCBF measurements by the clearance due to intercom-
partitional diffusion not only from adjacent tissue compartments, but also from cerebrospinal fluid space, we took steps to minimize this source of error by using only 3 to 5 min for H₂ equilibration and by using the initial slope method for calculation of rCBF. The relatively short period for H₂ saturation as well as the initial slope method of rCBF calculation would tend to minimize the contribution of the slow flow compartments.

In our model, the emboli ranged between 100 and 200 μm in diam which is larger than the 35 to 80 μm microspheres used in previous studies of cerebral embolism in the rat. However, unlike rigid microspheres, blood clots are not only soft enough to contract with pulsatile pressure, but may also fragment after embolization. The location of the embolic clots was variable, but the ipsilateral MCA territory was
consistent involvement. Kogure et al reported that all microspheres lodged in the ipsilateral hemisphere after internal carotid injection in rats whereas others reported that more than 15% were distributed in the contralateral hemisphere. In our study, contralateral embolic clots were found in 30% of the rats which may be related to the injection conditions.

Our angiographic studies showed that emboli initially occluding the internal carotid artery, soon migrated distally probably due to fragmentation. Clinically, migration and fragmentation of microemboli have been documented in the retinal circulation in patients with amaurosis fugax, implicated in the pathogenesis of transient ischemic attacks (TIA), and the disappearance of small vessel occlusion in stroke patients. We have observed spontaneous recanalization of occluded vessels on angiography in stroke patients. The fate of a thrombus, whether dissolving and migrating distally, or organizing in situ, may be related to hemodynamic factors, to properties of the thrombus, or to atheromatous changes in the intima. A blood clot produced by extravascular coagulation is histologically different from a thrombus formed intravascularly in the circulation. In our study, distal migration or fragmentation of the embolized blood clots may be partly due to the properties of the blood clot and to a lack of atheromatous changes of the intima in the young adult rat.

Compared with other microsphere models in rats, the magnitude of the insult in our model appears to be more severe, at least within 1 hour postembolism which may be related to the amount of embolic material used. Also, in our model, the pterygopalatine artery was permanently occluded to direct the emboli to the intracranial arteries. Whereas we observed gradual recovery of the EEG and rCBF after 10 to 30 min postembolism, in the microsphere models, brain edema or dysfunction gradually developed postinsult. This difference may be because of the difference in the embolic material.

Compared with a surgical occlusion model of MCA in the rat, the infarction in this embolic model is larger and more severe, but does not require a craniectomy which may cause physiological and biochemical artefacts. The embolization model may produce more serious ischemia than ligation or arterial clipping because it does not permit anastomosis via perforating arteries. Recently, Okada et al reported that MCA occlusion by silicone cylinder embolization caused more severe ischemia than surgical occlusion.

Evans blue leakage occurred in the basal ganglia in about 50% of the rats whereas it occurred in the cerebral cortex of only one rat. In rodents, cortical arterial collaterals are known to exist via leptomeningeal anas-
tomosis and distal collaterals from the three major cerebral arteries,\textsuperscript{17} while arterial collaterals in the basal ganglia are poorly developed. Thus, in the embolic model, the ischemic insult may be more severe in the basal ganglia. The distal migration and recanalization of the arterial supply may allow the leakage of the dye across the blood-brain-barrier.

In the unilateral proximal embolism group, both the mean rCBF and EEG power spectral of the embolized side remained depressed. When rCBF remained below 20 ml $\cdot$ 100g$^{-1}$ $\cdot$ min$^{-1}$ for 3 to 4 hours, infarction invariably occurred and rCBF, EEG and infarction were well correlated. This infarction threshold is higher than reported in previous studies.\textsuperscript{18-20} but may be influenced by the anesthetic, the method of ischemia, the duration of ischemia, and species differences. We used light barbiturate anesthesia, which could attenuate the development of cerebral infarction. The 3 to 4 hours of ischemia used, was longer than in previous studies.\textsuperscript{18-20} Furthermore, the neuron-glial ratio in the rat is higher than in the cat or monkey brain and may therefore require higher rCBF to maintain nerve cell function and viability.

In the unilateral peripheral embolism group, the embolized cortex was reperfused during the study, possibly due to the distal migration of fragmentation of the embolic clots. After 120 min postembolism, rCBF in the embolized side was restored to over 40 ml $\cdot$ 100g$^{-1}$ $\cdot$ min$^{-1}$ and was not different to the contralateral side. When reperfusion occurred after 1 to 2 hours of ischemia, electrical failure persisted despite an apparent tendency to recover. Thus, even with restoration of rCBF, recovery from electrical failure may be delayed. Previous studies\textsuperscript{21,22} show that during recirculation after transient ischemia, derangements in neurotransmitters recover slowly and effects on brain monoamines persist.\textsuperscript{21} Sundt and Michenfelder\textsuperscript{23} showed a
close correlation between brain ATP and lactate and EEG activity and rCBF during the early period of ischemia by MCA occlusion in the squirrel monkey. Upon clip release, there was prompt reactive hyperemia. However, after restoration of flow, there was a gradual increase in ATP, decrease in lactate and the EEG gradually returned toward normal. Our findings are similar, but we did not observe postischemic hyperemia or luxury perfusion which may be due to differences in the method of ischemia. In the embolic model, reperfusion occurs stepwise by improvement with distal migration.

Our model of brain infarction is relevant to the study of evaluation of thrombolytic drugs (urokinase, streptokinase, etc.) Modification may be introduced in preparing embolic clots. If reduced doses of embolic clots are used, it might be a model for transient ischemic attacks. Furthermore, it could be applied to studies on cerebral abscesses or tumor implantation in the brain if infected materials or tumor cells are used as emboli, respectively.

Acknowledgments

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