Production of Various Models of Cerebral Infarction in the Dog by Means of Occlusion of Intracranial Trunk Arteries

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SUMMARY Using the dog, which has been believed unsuitable for research on brain infarction because of an extensive collateral cerebral circulation, we have succeeded in producing at will ischemic foci, as determined from post-occlusion carbon perfusion, in the thalamus, cerebral mantle or entire cerebral hemisphere. This has been achieved by occlusion of various combinations of cerebral vessels at the base of the brain. A unilateral temporal approach has been used in identifying and occluding all of the bilateral trunk arteries. The following models of cerebral infarction have been made: 1) unilateral or bilateral complete cerebral hemisphere infarction, 2) unilateral or bilateral cerebral mantle infarction, 3) unilateral or bilateral thalamic infarction, 4) unilateral hemispheric and contralateral cerebral mantle infarction, 5) unilateral cerebral mantle and contralateral thalamic infarction, and 6) unilateral complete cerebral hemisphere and contralateral cerebral mantle infarction. These models of infarction in the dog can be produced with a high degree of success, and the amount of infarction can be controlled by the duration of vessel occlusion. The pathophysiology of brain infarction and brain edema following recirculation can be hemodynamically, electroencephalographically and biochemically studied using these models of cerebral infarction.

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although cerebral infarction is common, research on the pathophysiology of brain and hemodynamics following infarction is not advanced. One of the reasons is the difficulty in developing an ideal experimental model for cerebral infarction. An ideal experimental model would require the following features: 1) simple and inexpensive production, 2) a minimum number of non-specific anomalies of the cerebral vessels, 3) a high rate of production of uniform infarctic foci at fixed sites, 4) the ability to control the degree of infarction, 5) cerebral infarction in which the effects of drugs can be accurately determined and 6) the ability to maintain chronic preparations.

We have reported our experimental model in dogs in which control of the simultaneous occlusion of intracranial trunk arteries allows control of the degree of infarction within the anterior portion of the thalamus at a consistently high rate. The current work describes the production of various models of cerebral infarction as determined by post-occlusion carbon perfusion. These were produced by a unilateral temporal approach, together with various combinations of vessel occlusion.

Experimental Methods

Method of Producing the Experimental Model

Adult mongrel dogs, weighing approximately 10 kg were used. After severing the right zygomatic arch following the venous administration of thiopental sodium (Ravonal, 25 mg/kg), a temporal craniectomy was performed. To facilitate observation of the base of the brain, the cranium was opened widely, including the middle and frontal fossae. Following dural incision, the base of the brain was visualized using a surgical microscope and the arachnoid membrane around the blood vessels removed. The internal carotid artery (ICA) and A1 portion of the anterior cerebral artery (ACA) were identified, together with the ophthalmic, ethmoidal, A1 portion of the ACA, middle cerebral (MCA), posterior communicating (PComA), posterior cerebral (PCA) and anterior cerebellar arteries. When necessary, the cerebral contralateral arteries were identified. To produce the infarction models Scoville aneurysmal clips were simultaneously placed on combinations of arteries (fig. 1).

Carbon Perfusion

With each of the cerebral arteries still occluded, the descending aorta and bilateral jugular veins were exposed. A catheter with a 5 mm internal diameter was threaded into the thoracic aorta and immobilized. When artificial ventilation was begun, the thorax was opened and the aorta clamped directly above the heart, simultaneously with severance of the jugular veins and the beginning of perfusion. The perfusate was placed 150 cm above the dog's thorax and 300 cc of physiological saline was perfused, followed by 300 cc of the carbon suspension (10% soot, 9.5% gelatin, 1.3% phenol) mixed with 10% formalin, and, finally, the carbon suspension alone. A total of 500 cc carbon suspension was perfused, followed immediately by brain removal and 10% formalin fixation of one week's duration. Six consecutive coronal sections 5 mm thick, centering on the optic chiasma, were prepared and the location of carbon defects investigated in relation to the vessels which were
FIGURE 1. Relationship between occluded arteries in the brain of the dog and various kinds of models of cerebral infarction. Occluded arteries: 1) A\textsubscript{4} portion of ACA, 2) ACA bifurcation ethmoidal, 3) ACA bifurcation ophthalmic, 4) internal carotid, 5) MCA, 6) PComA, 7) PCA bifurcation PComA, 8) anterior cerebellar. Models of cerebral infarction indicating occluded arteries: 1) anterior thalamic infarction (occluded arteries, 3,4,5,6), 2) extensive thalamic infarction (3,4,5,7), 3) cerebral mantle infarction (1,2,3,5,7,8), 4) complete cerebral hemisphere (1,2,3,4,5,7,8), 5) incomplete cerebral hemisphere infarction (1,2,4,7,8), 6) bilateral cerebral infarction (combination of the above-mentioned arteries bilaterally).

Experimental Results

Anterior Thalamic Infarction Model

A carbon defect limited to the anterior thalamus of dogs was found following simultaneous occlusion of 4 arteries: the ICA, ACA, MCA and PComA. Details concerning this model, including histopathological findings, have been previously reported.

Extensive Thalamic Infarction Model

The occluded arteries in this model are identical to those of the anterior thalamic infarction model, but the occlusion site on the PComA is further posterior at the bifurcation of the posterior cerebral artery. The carbon perfusion defect was found in a wide area of the thalamus and hypothalamus on the occluded side (fig. 3).

Cerebral Mantle Infarction Model

The carbon perfusion defect is produced unilaterally in the cerebral cortex, subcortex and basal ganglia following the simultaneous arterial occlusion at 6 sites: the MCA, the point of bifurcation of the A\textsubscript{4} portion of the ACA and the ophthalmic artery and that of the ethmoidal artery, the A\textsubscript{3} portion of the ACA, PCA and anterior cerebellar artery. No perfusion defect is found in the thalamus or hypothalamus (fig. 4).

Complete Cerebral Hemisphere Infarction Model

A carbon perfusion defect can be produced throughout the unilateral cerebral hemisphere following simultaneous occlusion of arteries at 7 sites: the ICA, point of bifurcation of the A\textsubscript{4} portion of the ACA and the ophthalmic artery, and that of the ethmoidal artery, the A\textsubscript{3} portion of the ACA, MCA, point of bifurcation of the PCA and PComA, and anterior cerebellar artery (figs. 2 and 5).

Widespread, Incomplete Cerebral Hemisphere Infarction Model

An incomplete carbon defect in one cerebral hemisphere can be produced following the simultaneous occlusion of 5 arteries: the ICA, point of bifurcation of the A\textsubscript{4} portion of the ACA and the ethmoidal artery, the A\textsubscript{3} portion, point of bifurcation of the PCA and PComA, and anterior cerebellar artery. By means of opening only the ophthalmic artery, blood flow to the MCA, A\textsubscript{3} portion of the ACA and PComA can be re-established and sludging of the capillaries of the brain surface can be observed microscopically. Following carbon perfusion, a marked defect is not seen in the cerebral hemisphere on the occluded side, unlike the complete cerebral hemisphere infarction model, and the concentration of carbon black is low in comparison with the non-occluded side (fig. 6).

Various Experimental Models for Bilateral Cerebral Infarction Using Combinations of the Above Models

It is possible to identify and occlude all of the above-mentioned trunk arteries bilaterally using the unilateral temporal approach. Occlusion is facilitated by severing unilaterally the optic and oculomotor nerves. It is, therefore, possible to produce various combinations of the above models of cerebral infarction in both hemispheres by means of appropriate bilateral vessel occlusion. Specifically, the possible models are: bilateral extensive thalamic infarction...
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Figure 2. Model of complete cerebral hemisphere infarction frontal section. 1. 10 mm before the optic chiasma, 2. 5 mm before the optic chiasma, 3. passing through the optic chiasma, 4. 5 mm behind the optic chiasma, 5. 10 mm behind the optic chiasma, 6. 15 mm behind the optic chiasma.

Figure 3. Model for extensive thalamic infarction. Upper: the frontal slice at a point 5 mm behind the optic chiasma. Lower: the frontal slice at a point 10 mm behind the optic chiasma. Carbon defect (→)

Figure 4. Model for cerebral mantle infarction. Frontal slice taken at a point 10 mm behind the optic chiasma.

Discussion
Various animal models for producing complete cerebral infarction have been devised.1-4 These have (fig. 7), bilateral cerebral mantle infarction (fig. 8), unilateral cerebral mantle-contralateral extensive thalamic infarction, unilateral complete cerebral hemisphere-contralateral extensive thalamic infarction (fig. 9), etc.
included: 1) occlusion of all ascending vessels in the neck or thorax in mice, rabbits, cats, and monkeys, 2) occlusion together with intentional hypotension, and 3) unilateral cerebral hemisphere infarction in the Mongolian gerbil by means of unilateral carotid occlusion. The dog, because of its abundant collateral cerebral circulation, has not been used in experimental models for producing cerebral infarction using vessel occlusion.

We have found that, using a unilateral temporal craniotomy, the trunk arteries of the dog can be identified at the base of the brain. By means of occlusion of various combinations of these arteries, various models for cerebral infarction can be produced, as judged by carbon perfusion defects localized in the thalamus, cerebral mantle, or the entire cerebral hemisphere. Using a surgical microscope and depending upon the precision of the operation itself, these models in the dog can be produced without damaging the brain itself. We have found that with minimum practice, bilateral occlusion of the arteries of the base of the brain is relatively easy using a unilateral surgical approach. It is possible that carbon perfusion defect could occur due to the disturbances caused by surgery, but in sham operations in which cerebral vessels were identified unilaterally or bilaterally and handled but not occluded, no sign of a carbon perfusion defect was seen. Sham operations involving handling of the A2 portion of the ACA also did not result in a carbon perfusion defect. This was found despite the fact that primary difficulty in the operative procedure is in occlusion of the A2 portion of the ACA, which must be approached blindly in some cases, judging occlusion solely from the changes in
blood flow on the surface of the brain using a surgical microscope.

Although production of complete ischemia in a cerebral hemisphere was impossible at the outset of these experiments, we found that it could be achieved consistently by means of occlusion of the ACA, MCA and PCA, together with the ophthalmic artery, ethmoidal artery and cerebellar artery. The model of widespread incomplete cerebral hemisphere differs from the complete cerebral hemisphere infarction model because of opening only the ophthalmic artery and allowing blood flow to the MCA, A, portion of the ACA and PComA to be reestablished. This model allows investigation of the flow of administered drugs within a cerebral hemisphere.

Successful infarction of the anterior thalamus was obtainable in roughly 2/3 of the animals. Together with recording of the thalamic EEG, it has been possible to produce such infarctions in nearly 100% of the dogs, as we have previously reported. High rates of successful infarction in the other models have also been achieved.

No brain edema was observable through bone windows after vessels were still occluded in any of the models, including the complete hemisphere infarction model for periods of 4–6 hours. After release of vessel occlusion, no brain edema was observed following occlusion of 30 minutes or less. With the exception of the model for anterior thalamic infarction, edema was regularly observed after recirculation following occlusion of 60 or 120 minutes. It is believed that there are time limitations in the use of these models in research on brain infarction, except for the model for anterior thalamic infarction in which the infarction is small enough for prolonged survival.

Because it is possible to produce a large number of combinations of areas of infarction of varying severity, at various sites, unilateral or bilateral, these dog models may play an important role in helping to solve some of the remaining problems in the pathology, anatomy, physiology, biochemistry, and pharmacology of the cerebral infarction and postischemic brain edema.

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