Comparative Histopathologic Consequences of Photothrombotic Occlusion of the Distal Middle Cerebral Artery in Sprague-Dawley and Wistar Rats

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**Background and Purpose:** We have developed a minimally invasive model of photothrombotic occlusion of the distal middle cerebral artery in rats and have evaluated the patterns and features of the resulting histopathologic injury in two normotensive strains.

**Methods:** Food-deprived male Sprague-Dawley (n=14) and Wistar (n=10) rats anesthetized with halothane/nitrous oxide underwent a small craniotomy to expose the right distal middle cerebral artery just above the rhinal fissure. The animals were injected intravenously with the photosensitizing dye rose bengal, and the distal middle cerebral artery was irradiated with light from an argon laser-activated dye laser at three separate points to induce thrombotic occlusion. The ipsilateral common carotid artery was then permanently occluded, and the contralateral common carotid artery was occluded for 60 minutes. Three days later, the brains were perfusion-fixed and prepared for histopathologic examination, and infarct volume was determined by quantitative planimetry.

**Results:** In Sprague-Dawley rats, a large consistent temporoparietal cortical infarct was observed; mean±SD infarct volume was 130.5±40.0 mm³ (coefficient of variation, 30.7%) and a relatively small adjacent zone of selective neuronal necrosis (“incomplete infarction”), amounting to only 9.1% of the total injury volume, was also seen. By contrast, Wistar rats had smaller and more variable cortical infarcts (volume, 48.4±26.9 mm³; coefficient of variation, 55.6%) but displayed a much more substantial zone of incomplete cortical infarction (volume, 20.8±10.1 mm³; 30.1% of the total injury volume). In neither strain was infarct size related to alterations of blood pressure. In both strains, infarcts were limited to the cortex, typically involving the parietal cortex, somatosensory cortex, and forelimb region. Three rats exhibited infarcts in the contralateral hemisphere.

**Conclusions:** This model has the advantages of necessitating only minimal surgery, allowing the dura to remain intact, and avoiding mechanical trauma to the brain surface. In Sprague-Dawley rats, the resulting large cortical infarct exhibited relatively small interanimal variation, making the model suitable, for example, for replicate studies of pharmacotherapy. In Wistar rats, the large zone of incomplete infarction, a unique feature heretofore undescribed in rodent models of permanent focal ischemia, lends the model to the study of the pathomechanisms underlying graded cortical ischemic injury. *(Stroke 1993;24:286–293)*

**Key Words** • animal models • cerebral arteries • thrombosis • rats

As the majority of clinical strokes are thrombotic or embolic in origin, the development of relevant animal models of focal ischemic infarction is important for the study of the pathophysiology of ischemic brain injury and for the evaluation of potential therapies. Previous models of focal cerebral ischemia, typically entailing mechanical occlusion of the middle cerebral artery (MCA), have been described in cats, dogs, rabbits, subhuman primates,1,2

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and rodents.3 Mechanical models of MCA occlusion often necessitate extensive surgery, involve opening of the dura (with the attendant perturbation of cerebrospinal fluid dynamics), and carry the risk of local trauma to the brain at the site of mechanically induced vessel occlusion.

We report here the development of a model of photothrombotic occlusion of the distal middle cerebral artery (dMCA), combined with common carotid artery

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Artery of the midline incision ventral and therapy with a small-animal respirator. Wistar, model more relevant to the human clinical setting of a platelet agglutinate.6,7 We have examined the effect of thrombus consisting entirely of a nonfibrin-stabilized platelet agglutinate.6,7

Photochemically

The CCAs were exposed bilaterally by a ventral midline incision in the neck. The sternocleidomastoid muscle was then retracted laterally to expose the underlying artery, which was dissected free and surrounded by a loop of PE-10 tubing contained within 20-mm segments of bilumen Silastic tubing. The animal was mounted in a stereotaxic head holder, and a 1.5-cm vertical incision was made midway between the right eye and the right ear, according to the procedure of Chen et al.3 The temporalis muscle was separated and retracted to expose the zygomatic and squamosal bones. Under an operating microscope (model 50T, Carl Zeiss, Inc., Thornwood, N.Y.), a burr hole 3 mm in diameter was made with a high-speed drill 1 mm rostral to the anterior junction of the zygomatic and squamosal bones, revealing the distal segment of the MCA above the rhinal fissure. Care was taken not to injure the dura.

Arterial blood pressure was recorded throughout the operative procedure via a pressure transducer and Gould 2400 polygraph recorder (Glen Burnie, Md.). Arterial blood gases were measured before dMCA occlusion, after dMCA occlusion, and after CCA occlusions and were maintained within normal physiological limits. Body temperature was monitored via a rectal probe and maintained at 37.0°C by means of a heating pad and a warming lamp over the rat’s body.

Photochemically Induced Distal Middle Cerebral Artery Occlusion

An argon laser–activated dye laser (Coherent Inc., Palo Alto, Calif.) tuned to 562 nm was used to irradiate the dMCA at a power of 20 mW. The right side of the stereotaxic frame was tilted upward by 10° in order for the laser to strike the vessel perpendicularly, and the beam was focused on the vessel through a spherical lens of 25 cm focal length. The dMCA was occluded in three steps. The total dose of rose bengal (15 mg/ml, 0.67 ml/kg body wt) was determined. One third of this dose was first injected intravenously through the femoral catheter, and a thrombus was produced distally at the Y-shaped juncture of the frontal and parietal branches of the MCA by focusing the laser at that site. An orange fluorescence was immediately observed in the irradiated dMCA segment; a white thrombus began to form within the fluorescent segment and gradually elongated distally, as has been reported previously,8 while the segment distal to the thrombus constricted. The thrombus was formed within 2–3 minutes. The laser beam was then moved to two additional sites just proximal and distal to the temporal MCA branch. Rose bengal was injected before each irradiation. After the third irradiation the vessel was inspected for complete occlusion, as evidenced by lack of blood flow (distal blanching) through the dMCA and the presence of thrombotic material in the vessel.

Following the third irradiation, both CCAs were occluded by tightening the snares for 60 minutes. The contralateral CCA was then released, and the ipsilateral CCA was occluded permanently with a 3-0 suture. The neck and head wounds were closed, the catheters were removed, and the animal was extubated and returned to its home cage when fully awake. Three additional Sprague-Dawley rats underwent sham operations; the above procedure, including the administration of rose bengal, was performed, but irradiation of the dMCA and occlusion of the CCAs were not carried out.

Histopathology

Three days after dMCA occlusion, the rats were anesthetized with 2% halothane and perfused transcardially with a mixture of 40% formaldehyde, glacial acetic acid, and methanol (FAM, 1:1:8 by volume). The perfused animals were decapitated and the heads immersed in FAM for 24 hours. The brains were then removed and processed for paraffin histopathology by methods described previously.9 Coronal sections 10 μm thick were prepared throughout the extent of the infarct and were stained with hematoxylin and eosin. Twelve coronal levels with easily identifiable anatomic landmarks were chosen from each brain for morphometric study. Figure 1 indicates the anteroposterior levels of these sections with respect to the bregma. At low power (×1), the infarcted area was well delineated in all rats as a zone of microscopic pallor containing necrotic eosinophilic neurons, pallor and homogenization of the neuropil, and incipient macrophage infiltration. Areas adjacent to the zone of infarction were also carefully examined for evidence of neuronal necrosis and alterations of the neuropil. At each level, the area of complete infarction was traced onto paper by one of the authors who was blinded to the strain of the animal, with the aid of a camera lucida attachment to a Nikon microscope (Tokyo, Japan). The total injury area, comprising the zones of both complete infarction and selective neuronal alterations, was also traced onto paper at each coronal level. Each drawing was then retraced onto a digitizing tablet (Summagraphics Corp., Seymour, Conn.) interfaced to a VAX minicomputer system, which computed areas at each coronal level. Areas of incomplete infarction (selective neuronal necrosis) were...
computed as the difference between the total injury area and the area of complete infarction. Volumes were derived by means of numerical integration of sequential areas. Rats that died during the 3-day period were not perfused and were excluded from the study.

Statistical Analysis

Volumes of total injury, complete infarction, and incomplete infarction were compared in the two strains by means of a nonpaired Student’s t test. Blood pressure was compared in the two strains at six points during the procedure by a split-plot analysis of variance. Blood pressure and infarct volume were correlated for each strain by means of a Pearson correlation comparing the infarct volume and the blood pressure at three times.

Results

Physiological Variables

Blood pressure did not differ significantly between the Sprague-Dawley and Wistar rats at any time during the vascular occlusion procedures (Table 1). Blood pressure rose significantly at the onset of CCA occlusion ($F_{1,10} = 3.76, p < 0.05$) and remained significantly elev-

| TABLE 1. Mean Arterial Blood Pressure in Two Rat Strains |
|-----------------|-----------------|
| Time            | Strain          |
|                 | Wistar          | Sprague-Dawley |
|                 | ($n = 10$)      | ($n = 14$)      |
| Middle cerebral artery occlusion Before | 100±13 | 93±7 |
| After           | 104±14 | 101±9 |
| Common carotid artery occlusion 0 min | 115±11* | 119±14* |
| 15 min          | 114±5  | 117±8 |
| 30 min          | 117±12 | 115±11 |
| 60 min          | 104±24 | 105±11 |

Values are mean±SD mm Hg. No significant differences were noted between strains. *$p < 0.05$ compared with previous value for that strain.

| TABLE 2. Arterial Blood Gases in Two Rat Strains |
|-----------------|-----------------|
| Parameter       | Strain          |
|                 | Wistar          | Sprague-Dawley |
| Before MCA O    |                 |                 |
| PO$_2$ (mm Hg)  | 141±36          | 149±26          |
| PCO$_2$ (mm Hg) | 37.8±4.4        | 36.6±3.5        |
| pH              | 7.53±0.41       | 7.50±0.90       |
| After MCA O     |                 |                 |
| PO$_2$ (mm Hg)  | 151±29          | 158±25          |
| PCO$_2$ (mm Hg) | 35.8±3.5        | 37.5±3.2        |
| pH              | 7.57±0.98       | 7.41±0.73       |
| 60 min after common carotid artery O | 169±64 | 147±57 |
| PO$_2$ (mm Hg)  |                  |                 |
| PCO$_2$ (mm Hg) |                  |                 |
| pH              | 7.55±0.32       | 7.50±1.31       |

Values are mean±SD. MCA, middle cerebral artery; O, occlusion. No significant differences were noted between strains.

vated throughout the 60-minute bilateral CCA occlusion period. In sham-operated control rats, blood pressure was unaltered throughout the observation period. Arterial blood gases showed no differences between strains and no significant alterations during MCA/CCA occlusions (Table 2).

Infarct Volume

Sprague-Dawley rats had significantly larger infarcts than did Wistar rats; mean±SD infarct volumes were 130.5±40.0 mm$^3$ and 48.4±26.9 mm$^3$, respectively ($t_{10}=5.45, p < 0.0001$). Sham-operated animals did not exhibit any infarcted area. The patterns of infarction were similar for each strain, with the maximal area of injury occurring at approximately 1.3 mm posterior to the bregma in both Sprague-Dawley and Wistar rats (Figure 1). Nonetheless, the area of damage was consistently larger throughout the anteroposterior extent of the infarct in Sprague-Dawley rats (Figure 1). Furthermore, the cortical infarct of Sprague-Dawley rats was consistent, with a coefficient of variation (CV, standard deviation/mean) of 30.7%. By contrast, Wistar rats exhibited much greater variability of infarct volume (CV of 55.6%).

In Wistar rats, cortical areas bordering sites of infarction commonly appeared abnormal when viewed at higher magnification (Figures 2A and 2B). In contrast to the total tissue necrosis seen with complete infarction, these areas displayed selective neuronal necrosis. Astrocytes and blood vessels appeared relatively intact. In addition, the macrophage response seen with complete infarction was not apparent at these sites. The degree of neuronal injury was somewhat variable and was associated with parenchymal vacuolation and pallor. This process was termed incomplete infarction, following others’ terminology. $^{10,11}$ Although superficial cortical layers were most commonly affected, foci of neuronal necrosis were also observed in the other cortical layers. In contrast to Wistar rats, Sprague-Dawley rats exhibited only a very thin rim of selective neuronal necrosis (Figures 2C and 2D).
The mean volume of incomplete infarction was substantially larger in Wistar rats (20.8±10.1 mm$^3$) than in Sprague-Dawley rats (13.0±6.6 mm$^3$, $t_{(19)} = -2.12$, $p<0.05$), as shown in Figure 3. Total injury volume (complete plus incomplete infarction) was 143.5±42.1 mm$^3$ and 69.2±32.4 mm$^3$ in Sprague-Dawley and Wistar rats, respectively. Thus, the volume of incomplete infarction accounted for fully 30.1% of the total injury volume in Wistar rats, but for only 9.1% in Sprague-Dawley rats (Figures 1 and 3).

By means of Zilles' atlas of the rat cortex, anatomic areas of injury could be identified on histological sections. The cortical injury as seen in representative coronal sections from each strain is depicted in Figure 4. Areas consistently infarcted in Sprague-Dawley rats included the ventral portion of the primary motor cortex, the primary somatosensory cortex (SI), the supplementary somatosensory cortex (SII), the forelimb region, and the hindlimb region, often with extension to the gustatory and agranular insular cortex as well. Areas consistently damaged in Wistar rats included the SI, the forelimb region, and the ventral portion of the hindlimb region. The area of incomplete infarction in Wistar rats typically extended dorsomedially and ventrally from the core infarct area (see Figure 4A) to include damage to the deeper cortical layers and, often, anterior frontal cortex areas 1 and 2 as well as the anterior forelimb region. There was no damage to the striatum or thalamus in any of these rats.

There was no significant relation demonstrated between blood pressure and infarct volume or between blood pressure and incomplete infarction volume in either strain, as revealed by Pearson correlations performed to compare infarct volume with blood pressure at three times during the surgical procedure (before

**FIGURE 2.** A: Coronal photomicrograph showing area of total tissue injury (complete+incomplete infarction) in Wistar rat, stained with hematoxylin and eosin (×25). B: Higher magnification of same section, depicting zone of incomplete infarction consisting of selective neuronal necrosis with normal-appearing neurons (arrowheads), astrocytes, and blood vessels (×990). C: Coronal photomicrograph of area of total tissue injury in Sprague-Dawley rat, stained with hematoxylin and eosin (×25). D: Higher magnification of same section, depicting sharp transition zone between infarcted and normal-appearing tissues (×990).

**FIGURE 3.** Plot of mean±SEM area of incomplete infarction alone for Wistar (■) and Sprague-Dawley (○) rats at 12 coronal levels. Note that Wistar rats have significantly larger area of incomplete infarction than do Sprague-Dawley rats and that these differences are greatest at coronal levels showing largest zones of infarction.
dMCA occlusion, just after CCA occlusions, and after 60 minutes of CCA occlusions).

Three Sprague-Dawley animals exhibited bilateral infarcts. Their data were excluded from the Sprague-Dawley group described above. The right-sided infarct volumes of these animals were comparable in size and variability (mean±SD volume, 139±34 mm³) to those of the rats exhibiting unilateral right-sided infarcts. The left-sided infarcts in these rats were smaller (mean±SD volume, 96±21 mm³) but encompassed the same cortical regions as did the unilateral infarcts and, in two of the three rats, also involved the dorsolateral striatum. These three animals did not differ physiologically from the other rats of the Sprague-Dawley group with respect to blood pressure or blood gases.

**Discussion**

The salient finding of this study is that the novel model of photothrombotic occlusion of the dMCA, in conjunction with CCA occlusions, produces large and consistent infarcts of the cerebral neocortex of Sprague-Dawley rats. By contrast, the same procedure, when carried out in Wistar rats, yields substantially smaller and more variable zones of complete infarction but significant volumes of incomplete infarction with selective neuronal necrosis. The interstrain difference in the extent of infarction could not be accounted for by differences in arterial blood pressure. Furthermore, there was no evidence of spontaneous reperfusion in either strain by direct observation of the occluded MCA. Previous MCA occlusion studies have also described smaller and more variable infarcts in Wistar rats than in other normotensive strains.5,13 These differences could be due in part to variation in the tone of collateral vessels.

It is difficult to compare the infarct volume resulting from photothrombotic occlusion of the dMCA in this series with that produced in previous studies using mechanical dMCA occlusion. Of the six reports of mechanical MCA occlusion, only one reported data on infarct volume,4 the others employing either infarct surface area measurements6,15,16 or other damage scales.17,18 Nonetheless, the pattern of cortical infarction observed in the present study was similar to that observed following mechanical dMCA occlusion,4,17 with damage limited to the neocortex, including consistent injury to the parietal cortex, SI, and forelimb regions and more variable damage to the hindlimb region, SII, and agranular insular cortex. By contrast, other studies employing mechanical dMCA occlusion in young Wistar rats12 and Sprague-Dawley rats17 found no infarct damage to the cortex. Neither of the latter studies, however, involved tandem occlusion of the CCA, as was carried out in the present investigation.

In their systematic study, Chen et al6 confirmed that carotid artery occlusions were necessary to produce infarction of the rat brain following dMCA occlusion, and they determined that the optimal method in terms of animal survival and maximal infarct size was achieved by combining dMCA occlusion with permanent ipsilateral and temporary contralateral CCA occlusions. This procedure was adopted by us in the present study. It is of interest that Chen et al6 employing mechanical MCA occlusion, also observed occasional small infarcts in the territory of the contralateral MCA. Thus, it is unlikely that these contralateral infaracts are due to emboli formed uniquely by the photothrombotic process. Alternatively, a redistribution of interhemispheric blood flow engendered by permanent ipsilateral CCA occlusion, possibly abetted by incomplete reopening of the contralateral CCA, may have decreased perfusion in MCA collaterals.16 This process, if present over a prolonged time, may conceivably have led to infarction.14
Factors unique to photothrombically induced vascular occlusion may have contributed to the size and consistency of cortical infarcts in the Sprague-Dawley rats of the present study.\textsuperscript{19,20} Other work from our laboratory has shown that photochemically induced thrombogenically activated blood from a donor rat, when infused into the carotid artery of a recipient rat, induces moderate hypoperfusion throughout the ipsilateral hemisphere.\textsuperscript{20} If photochemically induced dMCA thrombosis led to a similar phenomenon in the vascular field distal to the sites of thrombosis, this might diminish the potential for collateral circulation within the ischemic MCA territory and hence contribute to large, consistent infarcts.

The presence of a substantial zone of incomplete infarction in the Wistar rat is a finding unique among rodent models of permanent focal ischemia. This finding stands in contrast to other studies of MCA occlusion in the rat, which have described sharply margined zones of infarction the rim of which correlates closely with precipitous transitions of local cerebral blood flow (CBF) from the normal to the severely reduced.\textsuperscript{21} Similarly, pathological studies of human stroke cases have also described sharp transition zones between normal and classically infarcted brain tissue.\textsuperscript{22} In normoglycemic rats, Nedergaard and Diemer\textsuperscript{23} described narrow zones of selective neuronal injury, approximately 1 mm wide, lying peripheral to zones of necrosis, the physiological antecedent of which was thought to be recurrent spreading depression–like deflections of the DC potential in the cortical infarct rim during the first few hours after MCA occlusion\textsuperscript{24}—a phenomenon not observed in hyperglycemic rats, which exhibited sharp histological transitions between the zones of infarction and normal brain.

The sizable zone of incomplete infarction in the Wistar rat, representing almost one third of the total injury area, suggests the intriguing possibility that a state of intermediate metabolism and function may be capable of subacute or chronic persistence. This possibility contrasts with the more traditional notion of the ischemic penumbra as an acute tissue zone just peripheral to the region of dense ischemia, with somewhat higher levels of CBF, reduced electroencephalographic amplitude, and suppression of cortical evoked response yet having only minimal elevations of extracellular potassium activity.\textsuperscript{25–29} Strong et al\textsuperscript{20} described ischemic neuronal changes in the penumbral zone 2 hours after MCA occlusion, either scattered or within microfoci. Evidence from other studies\textsuperscript{31–33} suggests that tissue zones having “supracritical” levels of CBF may not succumb to ischemia of short duration but may nonetheless develop neuronal injury if these levels persist. Various morphological appearances of selective necrosis have been described as well by others in a primate MCA occlusion model.\textsuperscript{34} Nonetheless, little evidence has accumulated to suggest that penumbral conditions can persist chronically or give rise to substantial zones of “incomplete infarction,” although this possibility has been suggested by Lassen\textsuperscript{10} and colleagues.\textsuperscript{11}

Our observations raise some questions: What are the functional correlates of the zone of incomplete infarction? What antecedent metabolic and hemodynamic differences in the responses of Wistar versus Sprague-Dawley rats to the same focal ischemic insult can give rise to such diverse results? These questions point the way toward future mechanistic studies.

To summarize, the present model of photochemically induced occlusion of the dMCA offers several avenues for further exploration of the pathomechanisms of focal cerebral ischemia. In the Sprague-Dawley rat, this model produces consistent neocortical infarction with acceptable interanimal variability, making it well suited to studies of therapy or behavioral outcome. In the Wistar rat, the model offers the possibility of examining the pathomechanisms underlying incomplete infarction and determining the ultimate pathological fate of tissue so affected. The photothrombotic model of dMCA occlusion carries a low mortality rate (9% in the current study, falling to <1% with subsequent [unpublished] experience). The technique is straightforward to perform and animals survive well and are able to eat, drink, groom, and ambulate normally soon after surgery. Finally, the procedure is surgically less invasive and less traumatic than mechanical MCA occlusion, producing no local parenchymal damage at the site of laser irradiation. These features combine to make the photothrombotic occlusion of the dMCA model a useful and attractive one in investigating the pathophysiology and treatment of thrombotic infarction.

References

A new method to induce localized areas of necrosis in rat brains is described by Markgraf et al. The procedure includes a midline cerebral incision to expose both carotid arteries; a vertical incision midway between eye and ear to expose (via a bone hole) the distal segment of the ipsilateral middle cerebral artery (MCA); induction of an arterial thrombus in the MCA by activating with a laser beam a circulating xanthene dye (rose bengal); transient (60-minute) occlusion of the contralateral common carotid artery; and permanent occlusion of the ipsilateral common carotid artery.

All experiments (n = 24) were terminated after 3 days, and the volume of the brain lesions in the three groups (one control and two experimental) was compared: Sprague-Dawley rats had larger complete infarcts than those found in Wistar rats; incomplete cortical infarcts were larger in Wistar rats than in Sprague-Dawley rats. These differences could not be related to alterations in blood pressure.

These results bring up the issue of either “matura-
tion” or “completion” in the features of the lesion initiated by the occlusion of an intracranial artery. Working with rats in which the origin of a MCA is intrinsically occluded by the insertion of a nylon monofilament,1 Nagasawa and Kogure2 confirmed the existence of cerebral blood flow (CBF) changes appropriate to the area of the brain where an infarct develops about 72 hours after the arterial occlusion. Garcia et al3 have applied the same method to occlude the MCA and observed the following in 58 rats: growth of the ischemic lesion between 30 minutes and 6 hours, and then again between 6 and 72 hours. Dereski et al4 have noted a comparable evolution in rat brain lesions studied between 15 minutes and 30 days after the tandem occlusion of an MCA branch and the ipsilateral common carotid artery. Within the territory of the occluded artery, the extent of the histologic damage varied significantly from region to region.5 In addition to the progressive growth of the lesion, two types of cellular (neuronal and astrocytic) responses (acute and delayed) were noted in experiments of permanent, isolated MCA occlusion.3 Bolander et al5 and Persson et al6 have reported spontaneous fluctuations in regional CBF values after permanent MCA occlusion in rats; they have also suggested that the brain lesion may continue to expand several days after the arterial occlusion.6 Finally, Li et al7 working with the model of intrinsic MCA occlusion, reported that neurons located at the peripheral rim of the main ischemic lesion (the “penumbra” of Astrup et al8) express “stress proteins”; this seemingly results in the protection of these cells from the effects of focal ischemia. Could this “protection” be the result of an improved circulation made possible by large collateral connections?

In the model described by Markgraf et al the differences in the volume of the brain lesions could be explained by differences in the efficiency of the collateral circulation in the two strains of rats used. An explanation for the results obtained in these experiments could be that in Wistar rats the brain lesion (induced by the Markgraf method) does not fully mature until 3 or 4 days. This is something worth exploring further.

These and similar observations emphasize the need to continue working on the definition of the chronology and physiopathology of “incomplete infarctions” of the
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