by the Robinson group. Some rats have very large Evans blue leaks that are most likely a result of MCA occlusion. For most old rats, the thicker skull requires more drilling, and connective tissue about the vessel presents more resistance to dissection of the MCA making hemorrhage more likely than in younger rats. While the smaller lesions in older rats (734-852) are larger ($p < 0.05$) than for the younger rats (752-842), the size difference may be due to more surgical trauma in exposing the vessel or some age factor. Since neither the Robinson nor the Tamura group differentiated the size of the lesion due to surgery from the one due to the occlusion, a good comparison of data is not yet possible.

Very large infarcts (mean size > $60 \text{ mm}^2$) invariably occur after MCA occlusion above the rhinal fissure in young spontaneously hypertensive stroke-prone rats (SHRSP) but not normotensive controls and are reported in a forthcoming paper. Factors that may be involved are discussed more fully and include rat strain, age, blood pressure, location of the occlusion, altered cerebral metabolism, reduced blood flow due to inadequate or insufficient regulation of collaterals, and so forth. Therefore, a single factor or a multifactorial combination involving method of occlusion, metabolic, vascular structural or hemodynamic alterations with age may be responsible for infarcts after rapid MCA occlusion.

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**References**


**Cerebral Blood Flow in the Four-Vessel Occlusion Rat Model**

To the Editor:

In a recent article appearing in this Journal, Furlow reported measurements of regional cerebral blood flow (CBF) during four-vessel occlusion (4-vessel occlusion) in the rat. Since his results are substantially different from previously-published values, and since his experimental methods violate our original description of the model, we feel obliged to restate the nature and degree of blood flow changes attained when the correct experimental conditions are followed.

Four-vessel occlusion in the rat has proven to be a highly reproducible method to achieve reversible but near-total forebrain ischemia. As a result, the model has yielded a consistent pattern of morphological brain damage following transient ischemia, that correlates well with regional changes in glucose metabolism in high-energy metabolite levels. This method for producing forebrain ischemia in the rat has been adopted by a number of investigators, and in some cases it has been modified to meet the needs of the individual experiments. Unfortunately, in certain instances, such modifications have resulted in a failure to follow the criteria which identify animals meeting the definition of successful 4-vessel occlusion.

Briefly described, the method involves production of forebrain ischemia by permanent occlusion of the vertebral arteries in the anesthetized animal and then 24 hours later temporary occlusion of the common carotid arteries in the awake animal. Since the animals are awake it is possible to observe the behavioral response of every animal subjected to this procedure. Only animals that become unresponsive and completely lose their righting reflex for the duration of the carotid artery occlusion are accepted as meeting the definition of 4-vessel occlusion. Immediately after and just prior to terminating occlusion of the carotid arteries the animals are placed on their left and right sides and stimulated with a tail or hindpaw flick to assure complete, bilateral loss of the righting response. Animals that fail to meet this test are excluded from the study. Approximately 75% of Wistar rats (Hilltop Farms) show complete loss of the righting response upon 4-vessel occlusion. In those instances where the animals are to be paralyzed and mechanically ventilated during 4-vessel occlusion, the rapid appearance of an isoelectric EEG will, in most cases, assure severe forebrain ischemia. Dilatation of the pupils upon occlusion of the carotid arteries has also proven to be a useful criterion of successful 4-vessel occlusion in either awake or paralyzed animals. Thus every animal subjected to 4-vessel occlusion, whether awake or paralyzed-ventilated at the moment of carotid artery occlusion, must meet these specific criteria or be excluded from further study.

When the above criteria are strictly followed, cerebral blood flow is reduced to the level previously reported by us and reproduced in Table 1. When measured with $^{14}$C-iodoantipyrine, blood flow to most of the forebrain during 4-vessel occlusion is reduced to approximately 3% or less of control values, while blood flow to the diencephalon, cerebellum and brainstem ranges from 10% to 30% of control values. Ginsberg, using the same CBF tracer and similar criteria for selection of ischemic animals, reported virtually identical degrees of regional CBF reduction in awake rats during 4-vessel occlusion.

Furlow reported measurements of regional CBF in paralyzed-ventilated rats using both polarographic and radioactive tracer techniques. Normal values obtained with the hydrogen clearance method varied widely between the two normotensive control groups, and the absolute CBF values obtained with this method were substantially lower than his control values obtained with the $^{14}$C-iodoantipyrine method. For these reasons and because the hydrogen clearance method is relatively inaccurate in severely ischemic tissue, we will restrict our comments to the CBF values obtained with the $^{14}$C-iodoantipyrine method. Furlow reports that CBF to various forebrain regions was reduced to only 40-70% of control values during 4-vessel occlusion. We can state categorically that such animals will not show an isoelectric EEG and therefore do not conform to the definition of 4-vessel occlusion as originally described. Animals that maintain a partial righting response during 4-vessel occlusion and that appear behaviorally to be only lethargic or stuporous will

<table>
<thead>
<tr>
<th>Region</th>
<th>Control Rats</th>
<th>4-Vessel Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal neocortex</td>
<td>133 ± 8</td>
<td>1 ± 0.1</td>
</tr>
<tr>
<td>Parietal neocortex</td>
<td>140 ± 9</td>
<td>1 ± 0.2</td>
</tr>
<tr>
<td>Stryiatum</td>
<td>97 ± 3</td>
<td>1 ± 1</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>80 ± 4</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>Diencephalon</td>
<td>111 ± 10</td>
<td>11 ± 3</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>107 ± 12</td>
<td>17 ± 4</td>
</tr>
<tr>
<td>Brainstem</td>
<td>112 ± 14</td>
<td>30 ± 2</td>
</tr>
</tbody>
</table>

Values (derived from reference 2) represent mean ± SEM for the number of animals shown in parentheses.
To the Editor:

Closer to the equator, perhaps I took a more simplistic view of semantically meaningful blood flow through the dissecting microscope to be empty after electrocauterization. In animals subjected to successful 4-vessel occlusion, continued blood flow through the anterior spinal artery maintains cerebellar and brainstem blood flow at 15 and 30% of normal values respectively, but contributes little flow to the forebrain. 

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Editor's Note: The previous letter was submitted to the author for comment.
occlude the ipsilateral carotid is ascertained at the time of placement of
the ligatures. This method permits reversible arterial occlusion in a
highly reliable fashion that does not require visual confirmation.

In conclusion, I feel my analysis of brain blood flow is a fair charac­
terization of the effects of bilateral vertebrocarotid occlusion in the
Sprague-Dawley rat without the selection biases for "success" imposed
by Pulsinelli and co-workers. I do not wish to downplay the novelty and
potential utility of the Pulsinelli-Brierley model. It is certainly one of the
better models for producing cerebral ischemia in the rat, but like every
model it possesses idiosyncracies and limitations. I trust this discussion
aids in clarifying some of the details of the method so necessary for
overcoming such shortcomings.

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