Time Course of Cerebral Blood Flow and Histological Outcome After Focal Cerebral Ischemia in Rats

Antoine M. Hakim, MD, PhD; Matthew J. Hogan, MD, PhD; and Stirling Carpenter, MD

Background and Purpose: The relation between time-dependent changes in cerebral blood flow and the appearance of infarction after focal cerebral ischemia is still a matter for debate. The aim of this study was to measure perfusion after simultaneous occlusions of the left middle cerebral artery and ipsilateral common carotid artery in rats and correlate it with the timing and distribution of histological changes.

Methods: We studied histological and cerebral blood flow changes 5 minutes and 4, 24, and 48 hours after the onset of focal ischemia. Blood flow was determined autoradiographically using [14C]iodoantipyrine. A coronal template subdivided into regions of interest was applied to the autoradiographs and the histological data.

Results: In some regions of the nonoccluded hemisphere, cerebral blood flow 5 minutes after occlusion fell below 50% of normal. Many ischemic structures showed stable blood flow for 48 hours after occlusion, confirming that in this model reperfusion is minimal. Infarction occurred eventually in all areas in which blood flow at 5 minutes fell below 10% of that in control rats, but infarction appeared earlier in regions in which blood flow at 5 minutes was below 5% of that in control rats. When blood flow at 5 minutes rose above 12% of that in control rats, the occurrence of infarction became unpredictable.

Conclusions: Despite the general dependence of infarction on perfusion levels, blood flow was not a reliable indicator of those regions committed to infarction. (Stroke 1992;23:1138-1144)

KEY WORDS • cerebral blood flow • cerebral ischemia • histology • rats

A number of laboratories have studied middle cerebral artery (MCA) occlusion in rats. Until recently, the predominant concerns have been the precise MCA segment to be coagulated,1 the influence of the strain used,2 and variability in the location and incidence of the resulting infarction.1,3 More recently, the temporal profile of regional cerebral blood flow (CBF) and the histopathologic changes occurring after MCA occlusion have received some attention. Bolander and his colleagues4 showed that CBF was lowest during the hours following vascular occlusion but that many regions showed significant reperfusion. These workers also reported that brain regions in which CBF fell below 15% of normal infarcted while those in which CBF remained above 20% of normal did not. Our goal in studying the time-dependent changes in regional CBF and the rate of appearance of histological infarction was to determine if certain CBF levels or patterns committed a region to infarction while others allowed the region to remain viable for some time after MCA occlusion.

Materials and Methods

All measurements were performed in male Sprague-Dawley rats weighing 250 g that were allowed to breathe unassisted throughout the studies. Under halothane anesthesia, the left MCA was exposed using the method of Tamura et al.5 The ipsilateral common carotid artery (CCA) was also exposed. Ischemia resulted when ligation of the CCA immediately followed cautery of the MCA, which was coagulated from its junction with the olfactory tract to the inferior cerebral vein; the vessel was then transected. The arterial occlusions were maintained until decapitation 5 minutes or 4, 24, or 48 hours later (n = 5 or more per group). In the first two groups catheters were placed into one femoral vein and artery during the same anesthetic period, but in the latter two groups a second brief interval of anesthesia was necessary 4 hours before decapitation to allow blood sampling and measurement of the animal's physiological status. Control animals were either normal rats in which femoral catheters were placed but no cranial or neck surgery was performed or sham-operated rats in which all surgical procedures were completed except for cautery of the vessels. In the sham-operated group, the overlying dura was "cauterized" for the same duration as the vessels in the ischemic groups.

All rats were fasted overnight. Measurements of rectal temperature, mean arterial blood pressure (MABP), arterial blood gases, and plasma pH as well as...
the plasma glucose concentration were started immediately after MCA+CCA occlusion. In animals decapitated 5 minutes after the occlusion, MABP and rectal temperature were monitored constantly but the remaining physiological variables except plasma glucose concentration were measured once. For all other durations of occlusion, arterial blood gases were measured 3 hours and 1 hour before decapitation while MABP and rectal temperature were monitored constantly.

We used the method of Sakurada et al to determine CBF in ischemic, normal, and sham-operated control rats. One minute before decapitation, 30 μCi of [14C]iodoantipyrine (IAP; specific activity, 1.47 μCi/mmol; Amersham Corp., Arlington Heights, Ill.) in 1.8 ml saline was injected intravenously. The injection was programmed to result in a linear rise of IAP activity in free-flowing blood sampled from an arterial catheter. Upon decapitation, the brain was removed and frozen with liquid nitrogen. Twenty-micrometer sections were exposed to x-ray film (Kodak SB-5, Picker Int., Montreal, Canada) for 3 days. The IAP content of the tissue was measured with a microcomputer imaging device (Imaging Research Inc., St. Catharines, Canada) in regions of interest (ROIs) defined by templates as described below. The activity of each ROI was determined in at least three sections and averaged. Approximately 92 sections from each rat were exposed to film. This was done by systematically discarding six sections and capturing the seventh for measurement of the IAP concentration. Following every sixth section obtained for this determination, the adjacent section was removed for histological examination.

The cerebral regions at which the IAP concentration was measured were standardized. Four coronal levels were chosen and subdivided into 23 symmetrical ROIs representing left and mirror-image contralateral areas (Figure 1). These four coronal levels represented templates applied to all rats. In each rat the autoradiographic brain sections most closely matching these templates were selected and the templates were modified to fit the individual anatomy; the activity in the different ROIs was then read and compared with standards exposed along with the brain. Each brain structure was analyzed in at least three sections, and the average was used as the concentration in that ROI.

Approximately 16 brain sections were obtained from every rat for histological examination. Sections adjacent to those obtained for autoradiography were removed, mounted on glass slides, and soaked for at least 1 hour in a solution of 0.4 M sodium cacodylate (25 ml), 50% glutaraldehyde (4 ml), and distilled water (70 ml). The slides were then transferred into cacodylate buffer before staining with cresyl violet and were submitted to a pathologist who was not aware of the experimental details. The stained sections showed areas of decreased cresyl violet uptake, which have previously been correlated with morphological changes consistent with ischemic cell damage (hyperchromatic cytoplasmic clumping with irregular nuclear and cytoplasmic membranes). The presence of frank infarction in the brain sections examined was therefore defined as an area of decreased dye uptake. The pathologist outlined these areas onto standard anatomical representations at the same levels as the templates used for CBF determinations. These areas were then summed and mapped to obtain the average regional incidence of frank infarction.

Results

Table 1 shows the results of physiological measurements performed on control rats and those with various durations of MCA+CCA occlusion. The reported values are the last recorded before decapitating the animals. Measurements in the normal and sham-operated
Table 1. Physiological Variables After Simultaneous Middle Cerebral and Common Carotid Artery Occlusion in Rats

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham-operated controls</th>
<th>5 min (n=5)</th>
<th>4 hr (n=6)</th>
<th>24 hr (n=6)</th>
<th>48 hr (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>121±4</td>
<td>82±9*</td>
<td>97±15</td>
<td>98±8</td>
<td>122±4</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>37±1</td>
<td>61±6*</td>
<td>35±2</td>
<td>39±1</td>
<td>38±1</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>83±6</td>
<td>67±3*</td>
<td>89±3</td>
<td>99±5*</td>
<td>91±1</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.43±0.01</td>
<td>7.31±0.03*</td>
<td>7.42±0.01</td>
<td>7.42±0.01</td>
<td>7.40±0.01</td>
</tr>
<tr>
<td>Plasma glucose (mM)</td>
<td>–</td>
<td>7.2±1.5</td>
<td>9.1±1.9</td>
<td>8.9±3.8†</td>
<td>9.4±1.1</td>
</tr>
<tr>
<td>Rectal temperature (°C)</td>
<td>36.0±0</td>
<td>33.9±0.5</td>
<td>36.5±0</td>
<td>36.3±0</td>
<td>36.1±0</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
*p<0.025 different from controls by one-tailed comparison and Bonferroni correction.
†Value obtained from determinations in only three rats. Differences in plasma glucose and rectal temperature were not statistically tested.

Rats were compared and found to not differ. Data for the sham-operated rats are therefore shown in Table 1. Figure 2 shows representative autoradiographs in a sham-operated rat and animals with MCA+CCA occlusion. CBF depression in the nonoccluded hemisphere during the early phase of contralateral ischemia is evident. In the occluded hemisphere, some ROIs show a return in radioactivity with increasing duration of occlusion while others show no recovery.

Figure 3 shows regional CBF after various durations of occlusion in a number of ROIs in the nonoccluded hemisphere. Figure 4 portrays the same information for the occluded hemisphere. The ROIs were grouped to reflect CBF in the cingulate cortex, hippocampus, superior frontal cortex (ROI 2 in all templates), sensorimotor cortex, and basal ganglia. For clarity, these figures do not show error bars and are meant to convey only trends. In the nonoccluded hemisphere (Figure 3) 5
minutes of left MCA+CCA occlusion lowered CBF in all ROIs and suppressed the regional variation in this function, resulting in a flat curve without the "undulations" seen in the control group. CBF in this hemisphere rose slowly toward control values with increasing duration of occlusion. In the occluded hemisphere (Figure 4), the cingulate cortex and hippocampus showed a similar phenomenon of a time-dependent slow rise in CBF toward control values. In some ischemic cortical regions (e.g., the superior frontal cortex) an increase in CBF was obvious only 48 hours after MCA+CCA occlusion. In the sensorimotor cortex and basal ganglia CBF remained quite stable between 5 minutes and 48 hours after the occlusion.

Figure 5 shows the regional incidence of frank infarction at template level 2 in the groups examined 4 and 24 hours after MCA+CCA occlusion. Infarction was detected in the striatum superiorly in all rats and laterally in 80% 4 hours after occlusion, while a major portion of the overlying cortex showed infarction only 24 hours after the imposition of ischemia.

No infarct was noted in any rat ischemic for 5 minutes. In rats ischemic for 4 hours the brain sections caudal to level 2 were normal. At 24 hours after MCA+CCA occlusion infarction was more extensive, and sections corresponding to template level 3 showed involvement similar to that seen in Figure 5, while two of six rats showed a small cortical rim of infarction at template level 4. No significant differences in infarct size were noted between the groups examined after 24 and 48 hours of ischemia.

Table 2 lists mean±SEM CBF and the fraction of rats showing infarction in selected ROIs at various durations of ischemia. In ROI 2=5, where CBF at 5 minutes was 5.5% of that in control rats, all animals showed infarction within the superior aspect of the caudate as early as 4 hours after occlusion. In ROI 2=3, where CBF at 5 minutes was approximately 12% of that in control rats, infarction in the outer area was seen in all animals 24 hours after occlusion and extended to involve the entire area by 48 hours. In contrast, ROI 4=3, with a CBF at 5 minutes not different from that in ROI 2=3, showed a small zone of infarction in two of six rats 24 hours after occlusion.

In general, when CBF dropped to 5% of that in control rats infarction appeared at 4 hours after occlusion, while CBF declines to 10% of that in control rats postponed the appearance of histological infarction. Thus, infarction appeared earlier in ROIs with severe decreases in perfusion. At approximately 12% of control levels, the histological outcome became unpredictable.

**Discussion**

Occlusion of the MCA in rodents as a means of producing focal ischemia and infarction gained credibility with the work of Tamura and his colleagues. It soon became evident that a number of factors influenced the reproducibility of the resulting infarct. Brint et al showed that the spontaneously hypertensive rat developed the most extensive and most reproducible neocortical infarction in response to distal MCA+ipsilateral CCA occlusion, while Duverger and Mackenzie showed that the Fischer-344 rat developed the most reproducible infarct volumes in response to occlusion of the MCA proximal to the origin of the lenticulostrate artery.

It was Bederson and his colleagues who defined the histological consequences of coagulating the MCA in different locations and over different lengths. These workers concluded that to obtain absolutely reproducible infarct rates the MCA had to be occluded along a segment that started proximally at the olfactory tract.
FIGURE 5. Schematic representation of percent of rats showing infarction at 4 (left) and 24 (right) hours after left middle cerebral and common carotid artery occlusion superimposed on regions of interest at template level 2.

and extended to the intersection of the MCA with the inferior cerebral vein. We used this method and simultaneously occluded the ipsilateral CCA.

Our aim in occluding the CCA simultaneously with the MCA was to minimize reperfusion of the ischemic region in an attempt to correlate CBF with the rate of infarction. Bolander et al., who occluded the MCA along the same segment that we used but did not occlude the ipsilateral CCA, showed variable reperfusion of a number of regions, with CBF at 6 hours often threefold that at 20 minutes after occlusion. We believe our model avoids this confounding factor. As Figure 4 and Table 2 show, a number of ROIs in the ischemic caudate-putamen and the overlying cortex had a stable CBF for 48 hours. Areas of reperfusion were still present but were limited to the cingulate and adjacent superior frontal cortex. The stability of cortical CBF with simultaneous MCA+CCA occlusion was recently confirmed by Kaplan et al. The magnitude of the depression of CBF in the contralateral hemisphere 5 minutes after occlusion and its subsequent return to control levels was surprising; CBF fell by >50% in some regions (Figure 3). The equivalent occurrence in patients may well result in histological lesions in the hemisphere contralateral to the main ischemic region if preexisting processes had already depressed CBF.

Despite the stability of CBF in our model, we experienced the same difficulty as many others in correlating histological outcome to the changes in CBF. The method of histological assessment employed, including

<table>
<thead>
<tr>
<th>ROI</th>
<th>Sham-operated controls</th>
<th>5 min (n=5)</th>
<th>4 hr (n=6)</th>
<th>24 hr (n=6)</th>
<th>48 hr (n=6)</th>
</tr>
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<tbody>
<tr>
<td>2-1 (anterior cingulate gyrus)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBF (ml/100 g/min)</td>
<td>169±17</td>
<td>43±5*</td>
<td>49±4*</td>
<td>81±14*</td>
<td>103±14*</td>
</tr>
<tr>
<td>Infarction (%)</td>
<td>—</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-3 (lateral frontal cortex)</td>
<td></td>
<td></td>
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<tr>
<td>CBF (ml/100 g/min)</td>
<td>146±11</td>
<td>17±4*</td>
<td>20±4*</td>
<td>11±5*</td>
<td>18±5*</td>
</tr>
<tr>
<td>Infarction (%)</td>
<td>—</td>
<td>0</td>
<td>0</td>
<td>100†</td>
<td>100</td>
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<tr>
<td>2-4 (inferior frontal cortex)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CBF (ml/100 g/min)</td>
<td>123±6</td>
<td>12±3*</td>
<td>11±3*</td>
<td>6±2*</td>
<td>28±21*</td>
</tr>
<tr>
<td>Infarction (%)</td>
<td>—</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2-5 (dorsal caudate)</td>
<td></td>
<td></td>
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<tr>
<td>CBF (ml/100 g/min)</td>
<td>109±10</td>
<td>6±2*</td>
<td>5±1*</td>
<td>3±1*</td>
<td>23±19*</td>
</tr>
<tr>
<td>Infarction (%)</td>
<td>—</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>3-6 (hippocampus)</td>
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<tr>
<td>CBF (ml/100 g/min)</td>
<td>77±4</td>
<td>37±4*</td>
<td>51±5*</td>
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<td>61±6</td>
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<tr>
<td>Infarction (%)</td>
<td>—</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4-3 (posterior parietal cortex)</td>
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<tr>
<td>CBF (ml/100 g/min)</td>
<td>163±11</td>
<td>19±3*</td>
<td>20±4*</td>
<td>26±5*</td>
<td>65±12*</td>
</tr>
<tr>
<td>Infarction (%)</td>
<td>—</td>
<td>0</td>
<td>0</td>
<td>33</td>
<td>33</td>
</tr>
</tbody>
</table>

CBF, cerebral blood flow; ROI, region of interest.
*p<0.01 different from controls by one-tailed comparison including Bonferroni correction.
†Infarct in outer cortical layers in all animals and in inner layers in five.
the use of cresyl violet staining, has been found ideal for the determination of infarction. Bolander et al reported that when CBF fell to 15% of normal values infarction resulted, while areas in which CBF remained above 20% of normal did not become infarcted. We report a lower CBF threshold for infarction, with infarcts occurring reliably when CBF at 5 minutes after occlusion is below 10% of that in control rats. We also show in Figure 5 that infarction will be apparent earlier in the regions suffering severe reductions in CBF. Thus, while the lateral frontal cortex is committed to eventual infarction in our model, 4 hours after occlusion the region appears normal to a neuropathologist unaware of the details of the experiment. Nevertheless, the ultimate extent of infarction in a region does not seem to be predictable from a knowledge of the early postischemic CBF. As Table 2 shows, relative to control CBF the posterior parietal and lateral frontal cortices (ROIs 4=3 and 2=3, respectively) are perfused equally 5 minutes after occlusion, yet their incidences of infarction are quite different. This echoes the finding of Tyson et al, who reported that both normal and abnormal histology can be found in regions perfused at 24–34 ml/100 g/min. Thus, we conclude that while postischemic CBF may determine when a particular region will show infarction, it is not possible to use CBF as a reliable index of the infarct’s topography.

With time metabolic indexes may replace blood flow in predicting cell death and infarct extent. Presently, the emphasis in the literature is to determine the blood flow thresholds at which metabolic and membrane responses to ischemia are triggered. Mies et al have shown that protein synthesis is affected when CBF drops to 55 ml/100 g/min while the threshold for adenosine triphosphate increases with duration of ischemia. This indicates that protein synthesis, vital for cell survival, is very sensitive to mild oligemia. We have reported that in vivo binding to [3H]nimodipine may rapidly indicate those ischemic brain regions vulnerable to the development of infarction. In the same model of MCA+CCA occlusion, the superior and lateral caudate showed increased binding to [3H]nimodipine within 5 minutes after occlusion, but the volume was greater in the regions suffering severe reductions in CBF. Thus, while the lateral frontal cortex is committed to eventual infarction in our model, 4 hours after occlusion the region appears normal to a neuropathologist unaware of the details of the experiment. Nevertheless, the ultimate extent of infarction in a region does not seem to be predictable from a knowledge of the early postischemic CBF. As Table 2 shows, relative to control CBF the posterior parietal and lateral frontal cortices (ROIs 4=3 and 2=3, respectively) are perfused equally 5 minutes after occlusion, yet their incidences of infarction are quite different. This echoes the finding of Tyson et al, who reported that both normal and abnormal histology can be found in regions perfused at 24–34 ml/100 g/min. Thus, we conclude that while postischemic CBF may determine when a particular region will show infarction, it is not possible to use CBF as a reliable index of the infarct’s topography.

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