Reperfusion After Cerebral Ischemia: Influence of Duration of Ischemia

NICHOLAS V. TODD, F.R.C.S., PIERO PICOZZI, M.D., H. ALAN CROCKARD, F.R.C.S., AND RALPH ROSS RUSSELL, M.D., F.R.C.P.

SUMMARY The influence of the duration of ischemia on the pattern of cerebral blood flow in recirculation was studied in anesthetized rats. Severe incomplete cerebral ischemia (mean ischemic flow = 5.8 ± 0.4 ml/100 g/min) was produced by four-vessel occlusion and recirculation permitted after 15, 30 or 60 minutes ischemia. All three groups showed an immediate hyperemia followed by hypoperfusion. Hyperemia was maximal following 15 minutes ischemia and least pronounced following 60 minutes ischemia (p = 0.0249). Hypoperfusion started most quickly following 15 minutes ischemia and was delayed following 60 minutes ischemia (p < 0.001). In established hypoperfusion there was no difference in flow between the three groups. The possible mechanisms of these changes in flow are discussed.

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ly with a Statham P50 transducer and recorded on a
Lectromed chart recorder. Arterial blood was sampled
anaerobically in microhematocrit tubes (0.1 ml) and
PaCO₂, PaO₂ and pH were measured on a blood gas
analyzer (ABL30 Radiometer, Copenhagen). pH was
corrected where necessary by i.v. infusion of bicar-
bonate. Body temperature was maintained at 36.5 to
37.5°C by external warming. The hematocrit was mea-
sured at the end of the experiment.

With the vertebral arteries divided, cerebral ische-
mia was produced by bilateral carotid artery occlusion
using Scoville-Lewis aneurysm clips. Removal of the
carotid clips permitted recirculation.

rCBF

Six Teflon-coated platinum electrode (75 μ diam.)
were placed into specific cortical regions stereotac-
tically as described above and polarised at + 400 mV to
the reference electrode. CBF was measured by clear-
anance of hydrogen (approximately 4% hydrogen in the
inspired gas mixture). and the flow calculated by the
initial slope technique between 30 and 90 seconds.

Experimental Protocol (table 1)

A total of 48 animals were used. The study mea-
sured rCBF, brain edema and blood-brain barrier
(BBB) permeability in each animal. Brain edema and
BBB permeability measurements required sacrifice of
the animal and the results are reported in the accompa-
ying paper. Animals were divided into three experi-
mental groups:

Group A — ischemia = 15 mins, followed by recircu-
lation,
Group B — ischemia = 30 mins, followed by recircu-
lation,
Group C — ischemia = 60 mins, followed by recircu-
lation.

All animals were allowed to stabilise for 60 minutes
after surgery. Anesthesia was maintained at a constant
level (70% nitrous oxide, 30% oxygen, 0.5% halo-
thane). rCBF was measured before ischemia, through-
out ischemia and in recirculation at 5, 15, 30, 60, 120
and 180 minutes (or until sacrifice, if sooner). PaCO₂,
pH and PaO₂ were measured before each flow.

Statistical Analysis

The flow data were compared by analysis of vari-
ance, using the BMDP program package. Data reduc-
tion and analysis were performed on the University of
London CDC6600 computer.

Seven variables were used (Group + 6 electrodes,
for each animal). The electrode data were transformed
to give mean regional data.

At specified times in recirculation the design depen-
dants were 3 x 3 (frontal, parietal, occipital x
Groups A, B, C). The differences between the depen-
dants means were compared to an error term. The
degrees of freedom were calculated for independent
cases (i.e., for animals, rather than electrodes).

Results

Three groups of animals were compared. The three
groups were each of 16 animals made ischemic for
either 15, 30 or 60 minutes. In all groups ischemia was
followed by three hours reperfusion.

General Physiological Parameters (table 2)

Systemic arterial pressure PaCO₂, PaO₂, and system-
ic pH remained stable throughout the experiment.
Four-vessel occlusion did not lead to systemic meta-
bolic upset. On recirculation there was a slight reduc-
tion in systemic pH greater following 60 minutes
ischemia. This was corrected by i.v. infusion of bicar-
bonate and never required more than 1-2 mmol of
bicarbonate to return the systemic pH to normal limits.
Whole blood hematocrit lay between 0.45–0.40.

Cerebral Blood Flow (table 3)

Halothane concentration was maintained at 0.5% at
all times. There were differences in the pre-ischemic
CBF regionally (table 3). Mean cortical CBF before
ischemia was not significantly different between the
three experimental groups.

Forty-eight rats underwent four-vessel occlusion
and they all became ischemic. The hydrogen clearance
curve showed an equilibration phase in the first 45
seconds after carotid clipping and then settled to a
steady ischemic clearance which was maintained until
the clips were removed. The mean ischemic flow was
5.8 ± 0.4 mls/100 g/min (mean all cortical regions ±
S.E.M.). There were no significant differences be-
 tween the levels of flow regionally or between the
three experimental groups.

Removal of the carotid clips permitted reperfusion
and there was a similar pattern of reflow in all cortical
regions and in the three experimental groups (fig. 1).
There was an immediate increase in rCBF. After a
variable period of time this hyperemia was succeeded
by 'delayed hypoperfusion' with flows reduced below
control values. There were differences between the

<table>
<thead>
<tr>
<th>Experimental Design</th>
<th>30 mins</th>
<th>60 mins</th>
<th>180 mins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mins ischemia</td>
<td>n = 16</td>
<td>n = 16</td>
<td>n = 8 n = 4</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 mins ischemia</td>
<td>n = 16</td>
<td>n = 16</td>
<td>n = 8 n = 4</td>
</tr>
<tr>
<td>Group C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 mins ischemia</td>
<td>n = 16</td>
<td>n = 16</td>
<td>n = 8 n = 4</td>
</tr>
</tbody>
</table>

A total of 48 rats entered the study.

Four rats in each group were sacrificed at: end-ischemia (no
recirculation); 30 mins recirculation; 60 mins recirculation; 180
mins recirculation; for measurement of brain edema and BBB per-
meability (please see accompanying paper).

n = number of animals in each group at the time indicated; each
animal had 6 cortical electrodes.
### Table 2 General Physiological Parameters

<table>
<thead>
<tr>
<th>Duration of ischemia</th>
<th>Pre-ischemia</th>
<th>Ischemia</th>
<th>5 mins reperfusion</th>
<th>60 mins reperfusion</th>
<th>180 mins reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SAP (mm Hg)</td>
<td>PaCO₂ (mm Hg)</td>
<td>PaO₂ (mm Hg)</td>
<td>pH</td>
<td></td>
</tr>
<tr>
<td>15 mins</td>
<td>124 ± 3</td>
<td>38.9 ± 0.7</td>
<td>171 ± 18</td>
<td>7.374 ± 0.005</td>
<td></td>
</tr>
<tr>
<td>30 mins</td>
<td>121 ± 2</td>
<td>37.7 ± 0.7</td>
<td>158 ± 14</td>
<td>7.356 ± 0.010</td>
<td></td>
</tr>
<tr>
<td>60 mins</td>
<td>127 ± 3</td>
<td>40.8 ± 0.7</td>
<td>192 ± 20</td>
<td>7.380 ± 0.012</td>
<td></td>
</tr>
<tr>
<td>15 mins</td>
<td>120 ± 4</td>
<td>39.7 ± 0.6</td>
<td>161 ± 11</td>
<td>7.377 ± 0.016</td>
<td></td>
</tr>
<tr>
<td>30 mins</td>
<td>117 ± 3</td>
<td>38.5 ± 0.5</td>
<td>150 ± 7</td>
<td>7.367 ± 0.014</td>
<td></td>
</tr>
<tr>
<td>60 mins</td>
<td>126 ± 5</td>
<td>39.3 ± 0.4</td>
<td>175 ± 19</td>
<td>7.353 ± 0.017</td>
<td></td>
</tr>
<tr>
<td>15 mins</td>
<td>124 ± 3</td>
<td>42.2 ± 1.2</td>
<td>150 ± 7</td>
<td>7.343 ± 0.012</td>
<td></td>
</tr>
<tr>
<td>30 mins</td>
<td>123 ± 2</td>
<td>38.8 ± 1.0</td>
<td>142 ± 10</td>
<td>7.389 ± 0.021</td>
<td></td>
</tr>
<tr>
<td>60 mins</td>
<td>126 ± 4</td>
<td>41.0 ± 0.8</td>
<td>176 ± 22</td>
<td>7.390 ± 0.021</td>
<td></td>
</tr>
<tr>
<td>15 mins</td>
<td>126 ± 4</td>
<td>38.4 ± 1.1</td>
<td>149 ± 13</td>
<td>7.386 ± 0.010</td>
<td></td>
</tr>
<tr>
<td>30 mins</td>
<td>121 ± 2</td>
<td>39.2 ± 1.0</td>
<td>137 ± 8</td>
<td>7.388 ± 0.021</td>
<td></td>
</tr>
<tr>
<td>60 mins</td>
<td>132 ± 4</td>
<td>39.7 ± 1.0</td>
<td>161 ± 23</td>
<td>7.351 ± 0.029</td>
<td></td>
</tr>
<tr>
<td>15 mins</td>
<td>116 ± 3</td>
<td>38.0 ± 0.8</td>
<td>156 ± 15</td>
<td>7.392 ± 0.007</td>
<td></td>
</tr>
<tr>
<td>30 mins</td>
<td>120 ± 2</td>
<td>40.6 ± 1.5</td>
<td>136 ± 12</td>
<td>7.354 ± 0.017</td>
<td></td>
</tr>
<tr>
<td>60 mins</td>
<td>130 ± 3</td>
<td>38.7 ± 1.1</td>
<td>179 ± 18</td>
<td>7.344 ± 0.017</td>
<td></td>
</tr>
</tbody>
</table>

SAP = systemic arterial blood pressure. Values = mean ± SEM.

### Table 3 Post-Ischemic Cerebral Blood Flow — Rat Cortex

<table>
<thead>
<tr>
<th>Ischemic Time</th>
<th>Frontal</th>
<th>Parietal</th>
<th>Occipital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Ischemia</td>
<td>80 ± 5</td>
<td>93 ± 9</td>
<td>96 ± 9</td>
</tr>
<tr>
<td>Ischemia</td>
<td>5.5 ± 0.4</td>
<td>6.3 ± 0.9</td>
<td>5.8 ± 0.5</td>
</tr>
<tr>
<td>5 min</td>
<td>205 ± 10</td>
<td>173 ± 19</td>
<td>162 ± 15</td>
</tr>
<tr>
<td>15 min</td>
<td>86 ± 10</td>
<td>117 ± 13</td>
<td>162 ± 21</td>
</tr>
<tr>
<td>30 min</td>
<td>49 ± 5</td>
<td>56 ± 5</td>
<td>119 ± 14</td>
</tr>
<tr>
<td>60 min</td>
<td>44 ± 4</td>
<td>48 ± 4</td>
<td>69 ± 5</td>
</tr>
<tr>
<td>2 hrs</td>
<td>54 ± 6</td>
<td>60 ± 5</td>
<td>54 ± 8</td>
</tr>
<tr>
<td>3 hrs</td>
<td>46 ± 2</td>
<td>63 ± 6</td>
<td>55 ± 7</td>
</tr>
</tbody>
</table>

CBF ml/100 g/min in 3 cortical regions. Flows were measured at rest, during ischemia and during reperfusion (5, 15, 30, 60 min and 2, 3 hrs). Three experimental groups with ischemic times of 15, 30, 60 min followed by reperfusion. Results are mean ± SEM. For statistical analysis refer to text.

Three experimental groups in each of these phases of recirculation, and we have considered the data under the headings 1) no-reflow, 2) hyperemia, 3) duration of hyperemia and 4) hypoperfusion.

**No-Reflow**

On removal of the carotid clips there was an immediate clearance of any hydrogen still present in the brain. The first flow was measured at 5 minutes of recirculation and from a total of 210 electrodes in 36 rats, not one electrode failed to show reflow. Some brain regions failed to mount a typical hyperemia and this was related to the duration of the preceding ischemia. After 15 minutes ischemia, only 2.5% of electrodes showed flows lower than their pre-ischemic value. This increased to 11.7% after 30 minutes ischemia and to 15.7% after 60 minutes ischemia. Those regions that did not show post-ischemic hyperemia nevertheless followed a similar pattern of later reflow with a reduction in CBF until during hypoperfusion they were not separate from the group as a whole.

**Hyperemia (fig. 2)**

All brain regions and all three experimental groups showed post-ischemic hyperemia, defined as mean flows in recirculation significantly greater than pre-ischemic values. This hyperemia was always maximal immediately on recirculation (measured at 5 minutes) and it developed in the presence of a normal systemic blood pressure (mean = 124 mmHg). The data are shown in table 3. There were 35° of freedom. There was a significant group effect (F = 4.16; p = 0.0249) with peak hyperemia being greatest in Group A, least in Group C. There was also a site effect (F = 13.49; p < 0.001) with occipital flows being significantly reduced, compared to the frontal and parietal flow. The

FIGURE 1. CBF following cerebral ischemia. Pre-ischemic flow was $94 \pm 8$ ml/100 g/min (there was no significant difference between the three experimental groups). During ischemia, flow was reduced to $5.8 \pm 0.4$ ml/100 g/min. On reperfusion, there was an immediate hyperemia followed by delayed hypoperfusion in all groups. (a) 15 minutes ischemia, (b) 30 minutes ischemia, (c) 60 minutes ischemia. a — all flows significantly greater than pre-ischemic flows, ‘hyperemia’, $p < 0.01$, b — all flows significantly lower than pre-ischemic flow, ‘hypoperfusion’, $p < 0.01$.

Group and site effects were independent (site/group interaction, $F = 1.35; p = 0.261$).

Duration of Hyperemia (fig. 3)

There was not an abrupt change from hyperemia to hypoperfusion and we calculated the time for the hyperemic flow to reach control values for each electrode. There was no regional difference, so the regional data were summed to give a mean cortical value for each animal. The duration of hyperemia in the three groups was $A = 16.9 \pm 0.5$ mins; $B = 21.9 \pm 1.3$ mins; $C = 62.1 \pm 7.4$ mins (results = mean ± S.E.M.). Differences between the means were compared using one-way ANOVA ($p < 0.001$) and we concluded that longer ischemia prolonged post-ischemic hyperemia.

Delayed Hypoperfusion (fig. 4)

All three experimental groups and all brain regions showed hypoperfusion, i.e., a reduction in CBF to levels significantly lower than pre-ischemic values (table 3). There was a difference in the rate of onset of hypoperfusion as described above. During established hypoperfusion (at two and three hours recirculation) differences between design dependants, brain region
(‘site’) and the experimental groups were compared using analysis of variance. There were 11° of freedom each time. At 120 minutes recirculation, there was no group difference (F = 0.13; p = 0.878) and no site difference (F = 1.41; p = 0.130). Similar results were found at 180 minutes recirculation. Indeed in this study, during hypoperfusion, there was a remarkable similarity of flow, despite the differences in the duration of the preceding ischemia. These flows were approximately 65% of the pre-ischemic levels.

Discussion

The four-vessel occlusion model of Pulsinelli and Brierly23 is an important model of ischemia and it produces severe cerebral ischemia in the rat, without added systemic insults such as anoxia24 or hypotension.25 Our modification of the surgical technique allows us to see the vertebral vessels and to be sure that they are divided and all 48 rats in this study became ischemic when the carotid arteries were clipped. There was no post-operative selection of animals and the preparation was completed in one stage. The model is a most stable preparation with no significant change in systemic blood-pressure, PaCO₂, PaO₂ or pH during the course of the experiment (table 2).

Pre-ischemic flow values were not significantly different between the three experimental groups but there were significant differences in flow between the three brain regions and this probably reflects differences in local metabolic rate. The flow values are comparable with results obtained with hydrogen clearance and auto-radiography in anesthetised and awake rats.17, 19, 27, 28

During four-vessel occlusion, severe hemispheric ischemia was produced in all animals with an overall mean flow of 5.8 ± 0.4 mls/100 g/min (all groups and all regions). We selected three periods of ischemia, 15, 30 and 60 minutes (Groups A, B, C) giving a progressive increase in the duration of ischemia. The pattern of cerebral blood flow in recirculation was similar in the three experimental groups and our results confirm the view that the sequence ‘hyperemia-hypoperfusion’ is the rule following incomplete ischemia. We have extended this by demonstrating that the peak and duration of hyperemia were dependent upon the duration of incomplete cerebral ischemia, whereas flow during hypoperfusion appeared to be independent of the duration of the preceding ischemia.

Hyperemia occurred in all groups and in all brain regions. During ischemia, powerful vasodilator substances such as adenosine, K⁺, H⁺ and CO₂ accumulate20 and dilution of pial vessels has been confirmed by direct observation.31 Hyperemia represents flow in this dilated vascular bed, and it might be expected that there would be a maximal vasodilatation with even short periods of cerebral ischemia. The similarity of flow in the frontal and parietal cortices within each group was striking and this may represent a state of maximal vasodilatation. Flow was lower in the occipital cortex despite the same degree of ischemia, and this probably reflects a difference in effective arterial blood-pressure. In the four-vessel occlusion model, all cortical regions reperfuse from the carotid arteries and the occipital cortex is furthest from the ‘head’ of pressure. If this explanation is correct, it suggests that manipulation of the blood pressure in early recirculation may be a method of increasing or decreasing hyperemia. There were differences in the degree of hyperemia between the three experimental groups with Group A showing the fastest flow and Group C the slowest. If we assume maximal vasodilatation in all groups, then this difference in flow must be due to a difference in perfusion pressure (= systemic arterial pressure — intracranial pressure). Since arterial blood-pressure was the same, variations in perfusion pressure are probably accounted for by changes in intracranial pressure (ICP)15 which is associated with brain edema. We found the amount of edema to be greater with increasing duration of ischemia26 and this probably accounts for the reduction in post-ischemic hyperemia in Groups B & C.

We would therefore suggest that following incomplete ischemia, immediate hyperemia is the rule and that this is a consequence of maximal vasodilatation. Differences in hyperemic flow represent changes in perfusion pressure, either a change in systemic blood-pressure or ICP. After longer ischemia, the duration of hyperemia was prolonged. Metabolic vasodilator products produced during ischemia lead to post-ischemic vasodilatation. With prolonged ischemia, the volume of these products is greater and also the cellular mechanism necessary for their metabolism and/or excretion are probably damaged to a greater extent. It is therefore likely that the prolongation of hyperemia following longer ischemia is secondary to reduced clearance of vaso-active products.

We have shown that hypoperfusion started significantly sooner after short periods of ischemia. Although it is difficult to compare results from different species and different experimental methods, previous work tends to confirm this. Hypoperfusion starts about 15 to 20 minutes after five minutes global ischemia in the dog32; 40 minutes after 30 minutes global ischemia in the cat31 and about 80 minutes after 60 minutes global ischemia in the cat.34 Hypoperfusion occurred in our experiments despite maintenance of a normal systemic blood-pressure and PaCO₂ and must be due to an increase in vascular resistance. This may be caused by (I) intravascular, (II) extravascular, or (III) vascular factors.

Although intravascular stasis, (I), is important in the no-reflow phenomenon, it is difficult to postulate spontaneous sludging occurring after hyperemia, and thrombi cannot be demonstrated in the cerebral vessels after 30 minutes incomplete ischemia in the rat.31, 34 'Intracerebral squeeze' (II) or vascular compression from brain swelling is a potential mechanism of post-ischemic hypoperfusion.16-12 However, the changes in flow do not follow the known changes in brain water, and CBF is most consistently reduced at 1–4 hours of reperfusion,13 at a time when brain water is resolving.36 We could not correlate reduced post-ischemic CBF...
with brain edema. Hypoperfusion occurred soonest (Group A) where brain edema was least and was delayed (Group C) where brain edema was maximal. Equally at two hours recirculation, all groups showed the same hypoperfusion despite marked differences in brain edema. A more likely explanation is that these post-ischemic flow changes occur because of a recovery of vascular smooth muscle tone. This recovery occurred most quickly after short periods of ischemia (Group A) and was delayed following longer periods of ischemia (Group C). In contrast, when hypoperfusion is established, flow was reduced to 60–70% of control values in all cortical regions and was independent of the duration of the preceding ischemia.

What are the consequences of these post-ischemic circulatory disturbances? During severe ischemia, there is a rapid failure of cellular metabolism with accumulation of ADP, a drop in pH and ionic fluxes (K+, Na+, Ca2+) across the cellular membrane. On recirculation, there is an increase in oxygen and glucose availability and a gradual reversal of the pathological changes. Various workers have suggested that hyperemia is an important pre-requisite of return of cerebral function, others have emphasized its potentially harmful effect. Clearly, 'no-reflow' implies continuation of cerebral ischemia and hyperemia demonstrates patency of the vascular bed. However, the cerebral metabolic rate (CMR) is reduced in early recirculation and very fast flows are inappropriate to the metabolic needs. It would therefore appear that CBF and CMR are uncoupled in early recirculation.

The mechanism and consequences of post-ischemic hyperemia are not clear. The reduction in CBF may simply reflect a reduced CMR and this would imply CBF/CMR coupling during hypoperfusion. Some workers have shown a steady rise in post-ischemic CMR and it may be that CBF and CMR remain uncoupled in later recirculation. CBF/CMR coupling during hypoperfusion with relative hypoxia producing secondary neuronal damage. Although we did not measure CMR, we feel that CMR is unlikely to have been the same in our experimental groups. We found no difference in CBF between the three groups and we would suggest that CBF and CMR remain uncoupled during the phase of hypoperfusion. Further work is required to clarify this point and also to determine the mechanisms of post-ischemic hyperemia.

In conclusion, after incomplete cerebral ischemia there is an immediate hyperemia followed by hypoperfusion and these flow changes may reflect changes in vascular smooth muscle tone. Hyperemia is a consequence of reperfusion into a maximally vasodilated bed and is reduced following longer periods of ischemia where the ICP is raised. Hypoperfusion starts most quickly after the shortest period of ischemia and this may be due to a return of vascular tone. In established hypoperfusion, flow is 60 to 70% of control values, regardless of the duration of the preceding ischemia.

Acknowledgments
The authors are grateful for the technical help of Miss Kathryn Allen and Miss Caroline Williams, and to Miss Bridie McAttee for secretarial assistance.

References
Duration of Ischemia Influences the Development and Resolution of Ischemic Brain Edema

NICHOLAS V. TODD, F.R.C.S., PIERO PICOZZI, M.D., H. ALAN CROCKARD, F.R.C.S., AND RALPH W. ROSS RUSSELL, M.D., F.R.C.P.

SUMMARY The influence of the duration of ischemia on the development and resolution of post-ischemic brain edema (SG method) was studied in anesthetized rats. Edema developed during ischemia and the amount of edema was related to the duration of ischemia (r = 0.843, p < 0.001). With recirculation to three hours, the major determinant of the amount of edema was still the duration of the preceding ischemia (p < 0.001). Resolution of brain edema only occurred following fifteen minutes ischemia. Post-ischemic blood-brain barrier breakdown (14C-AIB, EB albumin) was greatest following longer ischemia. Where present, the BBB leakage was simultaneously to large and small molecules.

BRAIN SWELLING due to water accumulation is an important complication of cerebral ischemia and will frequently lead to trans-tentorial herniation and death.1-3 The amount of water accumulating during ischemia depends on the level of flow during ischemia4-5 and its duration,6,7 and on whether the ischemia is complete or incomplete.8 Restoration of blood flow to ischemic brain may improve outcome and operations to revascularize the ischemic brain have been devised. Unfortunately reperfusion may lead to an increase in brain water, occurring either immediately9,10 or later, when it is associated with breakdown of the blood-brain barrier and leakage of protein-rich fluid into the brain interstitial space.5

We have used the model of cerebral ischemia described earlier11 to measure cerebral blood flow (CBF), brain edema and blood-brain barrier (BBB) permeability quantitatively and on a regional basis in the same animal. This study examined the effect of increasing duration of ischemia on the development and resolution of brain edema and blood-brain barrier permeability in recirculation after temporary, severe cerebral ischemia.
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