Reperfusion of Focal Ischemia of Varying Duration: Postischemic Hyper- and Hypo-Perfusion

H. Traupe, E. Kruse and W.-D. Heiss

SUMMARY Reperfusion into focal ischemia was studied in 25 cats after middle cerebral artery (mca) occlusion of 15 min to 2 hours duration. Changes in cerebral blood flow (CBF) were followed with the hydrogen clearance method in the center and periphery of the ischemic lesion expected. Postischemic hyperperfusion was found often after 15 and 30 min ischemia and regularly after 60 min mca occlusion. It was followed by normal flow after 15 and 30 min occlusion and by postischemic hypoperfusion after 1 hour ischemia. After 2 hours occlusion hypoperfusion generally was not preceded by hyperperfusion. After 60 min ischemia hyperperfusion could not prevent the development of severe hypoperfusion, but often was accompanied by a marked flow reduction in the periphery of the mca territory. The data indicate that hyperperfusion after ischemic periods lasting 60 min and more induces hypoperfusion in the area itself and in neighbouring regions by affecting perfusion pressure and thereby may enlarge ischemic damage.

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EXPERIMENTAL OCCLUSION of the middle cerebral artery (mca) leads to an immediate and more or less severe decrease in flow in the central territory of the vessel, the peripheral regions being less involved. Depending on the experimental model used the local distribution of the flow reduction varies: mca occlusion in cats and squirrel monkeys causes irregular cessation of flow observable in the pial arteries and veins with stasis of formed elements, which may resolve in some vessels, but usually results in large infarcts with variable borders. In baboons a more graduated focal ischemia was observed with accentuation in the basal ganglia and Sylvian fissure. The spatial variation of ischemia was related to the pial network which differs from species to species and from individual to individual.

Without reopening of the mca, some reperfusion was seen in most studies of experimental infarcts. Reperfusion after arterial occlusion was also observed in humans by angiography. Reperfusion after permanent arterial occlusion is explained by the opening-up of a collateral circulation due to the development of a pressure gradient toward the territory of the occluded vessel or by thrombolysis.

In reversible mca occlusion the restoration of flow is accomplished by a sudden reperfusion into a tissue in which the vascular resistance has increased due to intra- and extravascularly developing pathologic mechanisms. Until now, such a model has been tested only in a few studies. The model can be used to study the effect of the duration of occlusion on the development and restoration of focal ischemia and to observe the flow before, during, and after the arterial occlusion using appropriate methods.

Compared to clinical situations the model simulates surgical revascularization for treatment of acute stroke or spontaneous reperfusion after lysis of embolic occlusion.

The purpose of these experiments was to determine the effect of transient ischemia of 15 min to 2 hours duration on a) the extent of reperfusion, b) the temporal pattern of flow changes, c) the interactions of blood flow in more or less involved brain regions, and d) the influence of hyperemic reactions on the course of reperfusion.

Methods

Preparation and Experimental Model

Adult cats, unselected as to age or sex, and in weight range 1.8 to 3.8 kg, were used. All animals were studied under general anesthesia which was induced with pentobarbital sodium, 30 mg/kg injected intraperitoneally. Tracheotomy was performed and polyethylene catheters were placed into the femoral vein, and through the femoral artery to the abdominal aorta for continuous monitoring of blood pressure. The cats were immobilized with Flaxedil®, in doses just adequate to cause respiratory paralysis and mechanically ventilated with a gas mixture containing 25% oxygen, sufficient carbon dioxide to maintain pCO₂ at 27 to 33 mm Hg (0% to 5%) and 67 to 73% nitrous oxide. The respirator was adjusted so that the cats remained normocapnic (pCO₂, 30 mm Hg) throughout the experiment. Arterial pCO₂, pO₂, and pH were measured frequently and mean arterial pressure was recorded continuously via the aortic catheter. All these parameters were steady throughout the experiments. Animals in which these values varied were deleted from the study. Body temperature was maintained at 37–38°C by the use of a heating device.

The heads of the cats were placed in a stereotactic frame. The mca was approached transorbitally and exposed at its origin with the aid of an operation microscope. A hook, polished electrolytically and prepared from an arteriographic cannula (18G) with slight modifications as described by Little, was inserted above the proximal segment of the mca. Small pieces of gelfoam, tissue glue and silastic sheetings were used to close the craniectomy. Then the orbit was filled with rapidly hardening epoxy cement. A short occluding
stylet was inserted into the occlusion device to prevent leakage of cerebrospinal fluid. Through the cannula a pre-formed blunt stylet of adequate length could be advanced to occlude the mca for various periods of time. Craniectomies were made on the left parietal bone dorsal to the coronal suture: one between the sagittal and coronal suture (exposing the lateral gyrus, referred to in the text as the peripheral recording size) and one at the same level behind the zygomatic bone (exposing the sylvian or ectosylvian gyrus as the central area of the mca territory).

Measurement of Local Cerebral Blood Flow

Cerebral blood flow was calculated from the tissue desaturation of inhaled hydrogen gas by the technique developed by AUkland et al.\textsuperscript{15} Recording electrodes were prepared from 70% platinum–30% iridium–wire 250 μ in diameter. The wire was electrolytically sharpened to a tip of about 10–80 μ and isolated with glass. The tips of the electrodes were left bare (0.5–1 mm in length) and platinized using platinum chloride.

One electrode was inserted into the sylvian or ectosylvian gyrus (area supplied by mca, "central area") and one into the lateral gyrus (area supposed to be supplied by the anterior cerebral artery, "periphery" of ischemic territory), the indifferent electrode was placed into the neck muscle of the cat. A polarizing voltage of 400 mV positive to the recording electrode was applied and compensated via a bridge circuit. The slow potential changes proportional to the concentrations of H\textsubscript{2}\textsuperscript{16} were dc amplified, passed through a low pass filter and recorded on a polygraph. To determine local cerebral blood flow (CBF) the cats were ventilated with 5 to 10% H\textsubscript{2} until the concentration of H\textsubscript{2} in brain tissue had reached a plateau. The inhalation of H\textsubscript{2} was discontinued and the desaturation curves of the tissue H\textsubscript{2} clearance followed on the polygraph. To prove monoexponential rate of clearance semilogarithmic paper was used. The CBF was calculated according to the equation \( f = \frac{0.693}{T} \times 2 \) ml/g/min.\textsuperscript{17} As described elsewhere,\textsuperscript{18} in 20 experiments CBF was measured additionally with the microsphere technique before, during, and after mca occlusion. However, tissue volumes necessary for microsphere counting were rather large, and heterogeneous flow values were averaged out. Therefore, these results were not further used for this study.

Measurements of CBF were carried out until reproducible values were maintained; only when this state had been acquired was the mca occlusion performed.

Results

Extent of Ischemia

Experiments were performed in 25 cats. The occlusion period was 15 min in 4 cats (fig. 1), 30 min in 5 cats (fig. 2), 60 min in 10 cats (fig. 3), and 120 min in 6 cats (fig. 4). The mean pre-occlusion flow values in the center (sylvian and ectosylvian gyrus) were 84.4 ± 29 ml/100 g/min and 73 ± 30 ml/100 g/min in the periphery (lateral gyrus). Due to the high interindividual variability of flow, pre-occlusion flow values were highest in the group with 30 min ischemia. However, these differences did not reach statistical significance. Significant ischemia after mca occlusion was seen in all 25 experiments (table 1). In 18 cases the reduction of flow was more severe in the center than in the periphery of the mca territory. In 6 cases the occlusion was

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1}
\caption{Regional cerebral blood flow (rCBF) values in the center and in the periphery of the territory supplied by the mca before, during, and after mca occlusion of 15 min (n = 4). On the line "occl." the flow values estimated immediately after mca occlusion are given, on the line "reop." the last flow values before mca reopening are shown.}
\end{figure}
equally effective in the periphery and in the center, but in one case the effect was more severe in the periphery than in the center. The mean decrease in flow was to $15.6 \pm 13 \text{ ml/100 g/min}$ (with $p < 0.0001$ significantly different from basal value) in the center and to $23.8 \pm 16$ (with $p < 0.0001$ significantly lower than basal value) in the periphery. In 5 experiments an increase in flow was observed in the periphery during occlusion. The data indicate a severe effect of mca occlusion on both the central mca territory and the more collateral region expected to be supplied by the anterior cerebral artery. Redistribution of blood during mca occlusion could be observed immediately in the microscope, presumably as a pressure-conditioned reaction. Whereas flow decrease was stable up to 1 hour of occlusion slight changes of flow were observed in 2 cats during 2 hours occlusion (fig. 4).

**Flow Changes After Reopening**

Reopening of the occlusion device in all experiments initiated rapid reperfusion. Reperfusion to normal flow values as well as to hyper- and hypoperfusion was observed. After 15 min occlusion, blood flow immediately returned to pre-occlusion values in 2 cases, and in the other 2 cases in which occlusion flow values were above 20 ml/100 g/min a transient rise in the central blood flow was seen. This was observed immediately (case 1, fig. 1) or, as in case 3 (fig. 1) 30 min after reopening. In the latter case hyperemia was first seen in the peripheral region and returned to normal when flow in the central region rose to 180 ml/100 g/min (200% of pre-occlusion value).

After 30 (4 cats) to 40 min (1 experiment) occlusion mca reopening resulted in 2 cases (No. 8, 9, fig. 2) in a significant and immediate hyperperfusion up to values of 250 ml/100 g/min: in case No. 8 (fig. 2) this reaction was seen in the center of the ischemic region, and case No. 9 (fig. 2) showed hyperperfusion in the central and peripheral region. In 3 other cases reperfusion was below the basal values.

In 10 cats the mca was occluded for 60 min (fig. 3). In 9 cats reopening led to significant hyperperfusion in the center which was paralleled by the same reaction in the peripheral zone in one case. In the remaining cat 17 (fig. 3) reperfusion reached the level of the pre-ischemic value. The maximal mean value of the flow in all cases after reopening was found to be $178 \pm 64 \text{ ml/100 g/min}$ in the center and $61.8 \pm 28 \text{ ml/100 g/min}$ in the periphery. Final measurements 60 min to 6 hours after cessation of 60 min ischemia demonstrated a decrease in flow to 80% of the basal values in the center and to 70% of the basal values in the periphery (fig. 3, table 1). Interactions between the 2 regions were found in 9 postischemic courses: When flow was highest in
the center flow reduction was seen in the border zone (fig. 3).

Reperfusion following a 2 hour ischemic period (fig. 4) in 6 cases led to hypoperfusion. A short-lasting rise in flow above the pre-occlusion value was seen once and in another case the pre-occlusion value was reached, in both cases a rapidly developing hypoperfusion ensued. One hour after reopening a mean decrease in flow to 63% in the center and to 52% in the periphery was seen. Interregional interactions with flow increase in one area at the cost of decreased perfusion in another area were seen twice during the time of occlusion (fig. 6).

Hyperperfusion

Hyperperfusion was predominantly observed in the center of ischemia: it occurred in 2 cats after 15 min ischemia, 2 cats after 30 min, and 2 cats after 120 min ischemia. Following 60 min of mca clamp 9 out of 10 cats showed hyperperfusion after reopening. Due to the high variability of the individual basal and postocclusion values mean flow was statistically significant above resting state only in the group after 60 min ischemia (table 1). However, averaging flow values masked the occurrence of hyperperfusion which can be observed in the individual flow patterns (figs. 1-3). Hyperperfusion reached its maximum 3 to 30 min after cessation of ischemia and lasted for 10 min to 4 hours. During hyperperfusion the mean flow increased by 96.7 ± 53 ml/100 g/min (range 24 to 220 ml/100 g/min) and was significantly above basal values (p < 0.05). Hyperperfusion was found with occlusion flows between 0 and 38 ml/100 g/min (mean value 15.5 ± 12.7). Basal values, ischemic flows, and extent of hyperperfusion were not correlated. Hyperperfusion in the anterior region was found only in 4 cases: then it was similar to the increase in the mca territory.

Effect of Transient mca Occlusion on Final Flow

Observation time after reopening of the mca ranged from 35 min to 6 hours (mean 114 ± 84 min). Final values measured 69 ± 34 min after cessation of 15 min ischemia revealed an average change of +24% in the center and of −10% in the periphery; 77 ± 38 min after cessation of 30 min ischemia mean flow in the center was 8% and in the periphery 6% below basal
REPERFUSION OF FOCAL ISCHEMIA OF VARYING DURATION/Traupe et al.

While the flow decrease 166 ± 108 min after cessation of 60 min ischemia can be seen in the individual cases of fig. 3, the mean values (in the center 20%, in the periphery 30% below basal value) were not significantly different from pre-occlusion values due to the high variability of the values. As indicated in table 1 final flow 86 ± 22 min after end of 120 min ischemia was significantly below basal values in the center (37%) and in the periphery (48%) of the mca territory. The data indicate that the final hypoperfusion after transient mca occlusion can be observed in the central as well as in the peripheral zones, independent

**FIGURE 4.** rCBF values before, during, and after mca occlusion of 120 min (n = 6). For details, see fig. 1.

<table>
<thead>
<tr>
<th>Duration of occlusion</th>
<th>N</th>
<th>Basal values</th>
<th>Occlusion values</th>
<th>Max. post. occl. values</th>
<th>Final values</th>
<th>Observation time after cessation of ischemia (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 min</td>
<td>4</td>
<td>c 75 ± 18</td>
<td>20 ± 13†</td>
<td>120 ± 73</td>
<td>93 ± 52</td>
<td>69 ± 34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p 71 ± 27</td>
<td>27 ± 10*</td>
<td>51 ± 18</td>
<td>64 ± 13</td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>5</td>
<td>c 104 ± 37</td>
<td>25 ± 14†</td>
<td>151 ± 81</td>
<td>96 ± 60</td>
<td>77 ± 38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p 93 ± 37</td>
<td>26 ± 15†</td>
<td>96 ± 77</td>
<td>87 ± 67</td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>10</td>
<td>c 85 ± 27</td>
<td>9 ± 10‡</td>
<td>178 ± 65‡</td>
<td>68 ± 26</td>
<td>166 ± 108</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p 74 ± 28</td>
<td>27 ± 20‡</td>
<td>62 ± 28</td>
<td>52 ± 22</td>
<td></td>
</tr>
<tr>
<td>120 min</td>
<td>6</td>
<td>c 73 ± 19</td>
<td>15 ± 10‡</td>
<td>74 ± 43</td>
<td>46 ± 17*</td>
<td>86 ± 22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p 56 ± 15</td>
<td>25 ± 9†</td>
<td>46 ± 21</td>
<td>29 ± 5†</td>
<td></td>
</tr>
</tbody>
</table>

Significant differences to basal values: *p < 0.05, †p < 0.01, ‡p < 0.001.
of a transient postischemic hyperperfusion. The postischemic hypoperfusion is only related to the time of occlusion and not to the degree of flow disturbance (fig. 5). The extent of postischemic hypoperfusion was not dependent on the duration of the experiment. As visible from the MABP values given in the figures flow changes were not related to alterations in blood pressure.

Discussion

Experimental Model

The model of reversible mca occlusion in cats as described above produces relatively large areas "where healthy blood does not circulate properly through the blood vessels." The hemodynamic plasticity in the distribution of the 3 major cerebral vessels in cats seems to be heavily reduced when the mca is segmentally occluded. Graduated ischemia expanding into the anterior cerebral artery (aca) as found generally in the study can be explained by the disproportion of the territories to be supplied: The inflow of blood is limited and collateral systems, as they share their capacity, fail to parry the trauma of mca occlusion. Redistribution during occlusion thus leads to a widespread zone of disturbed blood flow involving both the region of the aca and mca (the territory of the posterior cerebral artery was not studied). Reduced flow during mca occlusion measured over the gyrus suprasylvius and ectosylvius ranged between 0 and 40 ml/100 g/min and is sustained by pial anastomoses. These values are similar to those reported by others. So far the model is representative of a pathological state which presumably occurs in man in the center and in the border zone of an infarct. It may be used to examine sudden reperfusion of one cerebral artery as will happen after neurosurgical treatment, after lysis of emboli, or when collateral vessels come into play. When reperfusion is not achieved by collateralization, mca deocclusion shows immediate and vehement effects on the previous ischemic region. As shown previously duration of the experiments had no influence on flow values measured in our setup. Therefore, the influence of worsening physiologic parameters with time on our results ("bad brain" effect) can be ruled out.

Flow Measurements

The hydrogen clearance methods has the advantage to record flow in many small tissue volumina repeatedly at short intervals as the effective tissue washout. Fast changes of perfusion as occurring with mca occlusion and with the onset of post-ischemic hyperperfusion can be observed as an alteration in the clearance rate. While steady state conditions are not fulfilled with perfusion changes during H2-clearance, measurements have to be verified in repeat recordings. As a disadvantage the H2-clearance technique necessitates the insertion of platinum electrodes into the brain tissue. Therefore, usually open skull preparations are
used, prohibiting the development of intracranial pressure alterations.

**The Term "Hyperperfusion"**

The terms hyperperfusion, hyperemia, luxury perfusion, or cerebral vasomotor paralysis are frequently used synonymously. They must be differentiated according to the method used. Hyperperfusion describes the state when the local perfusion is raised, hyperemia is related only to local cerebral blood volume. The finding of hyperemia alone as seen in the superficial microvasculature of the cerebral cortex or in angiographic studies does not necessarily involve an increase in CBF. Only if both cerebral blood volume and transit time are measured\(^1\), \(^2\) a clear differentiation between hyperemia and hyperperfusion can be made. The "low perfusion hyperemia" observed during mca occlusion in closed skull studies\(^3\) was the result of extreme flaccidity of cerebral vessels being ballooned by collateral flow against the relative high venous outflow resistance: this is not comparable to the hyperemic or supernormal flow measured by others using the hydrogen technique. The luxury perfusion syndrome\(^2\) is specified by reddening of pial veins, reduced \(O_2\) consumption or reduced glucose consumption. The term should be used only if flow and metabolism are measured simultaneously.

**Postischemic Hyperperfusion**

In this study hyperperfusion was observed as the result of sudden anterograde reperfusion in one major cerebral vessel, the middle cerebral artery, after ischemia lasting for 15 to 60 min. As even shorter occlusion times down to one minute have caused hyperperfusion\(^4\) it is likely that such hyperperfusion is a common, physiologic reaction to short-lasting ischemia. Hyperperfusion following 15 to 30 min ischemia leads to normal flow. That hyperperfusion was not observed in all cases might be due to its duration which might lie below the temporal resolution of the \(H_2\) technique.

Hyperperfusion following ischemia of longer duration, in our experiments 60 min, seems to have no beneficial effect, neither on the brain regions where it develops nor on the surrounding tissue: it is followed by postischemic hypoperfusion and might induce flow reductions in neighboring brain regions. Though the decrease of flow during the ischemic period was comparable in both, the center and the periphery of the mca territory, hyperperfusion was observed predominantly in the center of the lesion. This demonstrates that the anterograde reperfusion exhausted itself in the most proximal dilated vascular bed.\(^5\) However, our data show that various flow patterns may develop in immediately neighboring brain areas with an increasing hyperperfusion in one and a simultaneously developing hypoperfusion in an other region, and such heterogeneities in flow were also observed autoradiographically.\(^6\) While such phenomena could be explained by different pressure gradients with paralytically dilated vessels in the center and increased vascular resistance in the periphery, interregional steal effects could also be responsible. It has been shown recently,\(^6\) that autoregulation and CO\(_2\)-reactivity is disturbed during hyperperfusion in the center as well as the periphery of the mca territory. Therefore, with impaired vascular reactivity neither the vessels in the center nor in the periphery are able to compensate for pressure changes. As hyperperfusion after ischemia of longer duration is always followed by hypoperfusion and the pressure gradients are changed concomitantly, alternating cycles may occur and spread out over the brain.\(^7\) Thereby, hyperperfusion may help to extend ischemic damage into primarily not-affected brain regions.

**Postischemic Hypoperfusion**

Hyperperfusion may be looked upon as a physiologic autoregulative overswing\(^8\) as long as it finally leads to normalization of flow. In our studies this is the case up to 30 min of ischemia. After mca occlusion of longer duration hyperperfusion in the previous center of ischemia is followed by hypoperfusion i.e. the primary low vascular resistance within the reperfused ischemic lesion increases.\(^9\) On the other hand, in the periphery of the mca territory hyperperfusion develops usually without preceding hyperperfusion. The pathomechanism of the postischemic hyperperfusion syndrome is not clear. Factors which may be involved are the narrowing of the capillary lumen by endothelial edema and "bleb" formation,\(^10\) imbibition of water from the intravascular to the extravascular space,\(^11\) changes in blood viscosity,\(^12\) brain swelling,\(^13\) vasospasms\(^14\) or red blood cell aggregation.\(^15\)

In late states after severe ischemia flow may be low due to decreased metabolic demands of damaged brain tissue.\(^15\) Hyperperfusion with flow 50% below basal values directly following reperfusion after 120 min ischemia could be due to the obstruction of about 50% of the capillaries ("no reflow phenomena.")\(^16\) During postischemic hypoperfusion the maintenance of blood flow is dependent on the remaining perfusion pressure. The obstruction can only be overcome if the intravascular pressure is high enough to disperse red blood cell aggregates and to keep open the compressed capillaries.

However, it is clear from our results that the postischemic hypoperfusion responsible for decreased oxygen availability in the brain tissue\(^17\), \(^18\), \(^19\) develops during reperfusion after 60 and 120 min of ischemia irrespective of preceding post-ischemic hyperperfusion, in the center as well as in the periphery of the territory supplied by the transiently occluded vessel. It remains to be shown whether slow reperfusion helps to ameliorate the final prognosis of focal ischemic lesions. This seems likely with regard to the clinical course of infarct patients who show neurological improvement during collateralization.

**References**

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