Recovery of the Cortical Evoked Response Following Temporary Middle Cerebral Artery Occlusion in Baboons: Relation to Local Blood Flow and $\text{PO}_2$

NEIL M. BRANSTON, PH.D., LINDSAY SYMON, F.RCS., AND H. A. CROCKARD, F.RCS.*

SUMMARY The degree of recovery of the somatosensory cortical evoked response following a period (15 to 65 minutes) of partial ischemia, produced by temporary occlusion of the middle cerebral artery (MCA), was assessed in baboons and related to the local tissue blood flow and $\text{PO}_2$ before, during and after the occlusion. Flow was measured using the technique of two-minute hydrogen clearance.

Failure of complete recovery of the evoked response was associated with significantly greater depths of ischemia and tissue hypoxia during occlusion, and with significantly greater and persisting tissue hypoxia after occlusion, than complete recovery. Complete recovery of the evoked response also was associated with tissue hyperoxia after occlusion. The reduced postocclusive $\text{PO}_2$ levels associated with incomplete recovery of the evoked response suggest that reduced perfusion during ischemia was sufficiently severe to cause some degree of irreversible anoxic damage. The effect of a brief (three to ten minutes) period of ventilation with air (instead of oxygen) under such low-flow conditions was to depress the evoked response significantly further; normally perfused brain, however, was unaffected by this procedure. This finding has clinical implications in regard to normobaric oxygen therapy.

Methods

Sixteen baboons (Papio cynocephalus) of either sex in the weight range 10 to 18 kg were prepared for measurement of the cortical evoked response to contralateral trigeminal (mandibular) stimulation and for polarographic measurement of both local tissue oxygen tension and flow (hydrogen clearance) at the site of the electrical recordings on the postcentral gyrus. Details of these techniques have been given elsewhere and may be summarized as follows. Anesthesia was maintained with alpha-chloralose (60 mg per kilogram i.v.), the animals were immobilized with gallamine triethiodide, and arterial $\text{PO}_2$ was controlled by pump ventilation of pure oxygen to within the normal range of 38 to 43 mm Hg. Arterial blood pressure, $\text{PCO}_2$, $\text{PO}_2$, and $\text{pH}$ were measured continually. The lateral aspect of the cerebral hemisphere was exposed and kept covered with a warmed mineral oil pool, platinum electrodes (with a polystyrene membrane in the case of the $\text{PO}_2$ electrodes) of diameter 300$\mu$m (pointed at the tip) were placed in the gray matter at appropriate positions for the polarography, and focal monopolar EPs were continuously recorded from the surface.

In each experiment, after a period of stabilization and control measurements, the MCA was occluded for a predetermined time using a small clip via a previously prepared transorbital approach. Apart from the first experiment in which the MCA clip was applied for 105 minutes, the durations of occlusion fell into two ranges: 15 to 31 minutes (mean = 19.1 minutes, SD = 6.8, N = nine animals) and 50 to 65 minutes (mean = 58.2 minutes, SD = 5.5, N = six...
animals). In seven animals, after a recovery interval following release of the clip, the artery was again occluded for a short period.

Measurements of the cortical EP (peak-to-peak amplitude of the primary positive/negative response), tissue PO2, and two-minute initial flow were made during each of three phases of an experiment, termed the control, clip and post-clip phases. The post-clip phase was defined as the period following release of an occlusion but before any further occlusion. The EP amplitude and PO2 data were expressed as percentages of their respective control values, while flow was measured in milliliters per 100 gm per minute.

At intervals during an experiment, the arterial PO2 was altered by switching from the normal pure oxygen ventilation to air ventilation at the same stroke volume and rate; arterial PO2 then dropped within a few minutes from its normal value greater than 350 torr to the range 60 to 100 torr, while arterial PCO2 was unaltered. During such an “air episode,” measurements were made on tissue as described above. The oxygen supply was reconnected after a period of three to ten minutes.

The statistical results given here were obtained using the paired or unpaired t-test, as appropriate. With the unpaired test, if the two populations did not satisfy the F-test for equality of variance, the Cochran approximation12 was used.

**Results**

Table 1 gives the basic tissue flow, PO2 and EP recovery data that were recorded during and after the first MCA occlusion in the 16 animals. The total time over which these variables were observed in the post-clip phase did not exceed 90 minutes.

**GENERAL CHARACTERISTICS OF EP RECOVERY IN THE POST-CLIP PHASE**

Two principal general features of recovery of the EP stand out and therefore have been taken as the basis of a common descriptive framework for recovery in all the experiments. First, when the MCA clip was removed, the immediate restoration of blood flow was paralleled by a rapid partial recovery of the EP within three minutes, and usually within the first minute. We have termed this the fast stage of recovery. (In one animal, the start of recovery was delayed by six minutes, flow restoration also being delayed.) This was followed by a further stage of recovery toward the control EP level, usually with a much slower time course, called the slow stage of recovery. Not all of the experiments showed both of these stages. An obvious fast stage was present in the recovery curves in 11 animals and a slow stage in 13. Recovery is illustrated in the example shown in figure 1a.

The second feature was that the time course of the slow stage of EP recovery could, in most cases, be well fitted by a monoexponential function, over the period of observation of the EP in the post-clip phase. Specifically, it was noted that a certain final level of recovery (different for each experiment) could be chosen such that the semilogarithmic plot of the difference between it and the recovery curve approximated, often remarkably well, to a straight line (fig. 1b). If the final level so projected was chosen too high or too low, the plot was no longer linear. Since this exponential form was clearly present in those cases where the EP recovered to control levels during the time of observation, it was thought reasonable to make the simplest inference, namely, that recovery was in general of exponential form. Accordingly, each of the slow recovery stages was analyzed by this exponential curve-fitting technique and characterized numerically by the asymptote (final recovery level, table 1) of its corresponding monoexponential. In no case, within the period of post-clip observation, was there any indication of an additional later stage of recovery which might suggest departure from the exponential form.

As table 1 shows, recovery of the EP to (or even above) control level either occurred within the actual post-clip observation time or was predicted to do so by the method just described, in six animals. Recovery was incomplete in

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**Figure 1 Recovery of the EP following temporary MCA occlusion.** In (a) is shown the typical time-course of return of EP amplitude toward control level in the post-clip phase. The quantity y, which is the difference between EP amplitude and projected final recovery level at any given time, is shown in (b) plotted against the same time scale but in semilogarithmic coordinates. Linearity of the log y plot indicates the exponential form of the recovery curve. In this example, recovery was incomplete since the final recovery level was less than control. The associated local blood flow is shown in (c).
nine animals, the final level ranging from 43% to 83% of control, while in the remaining case the observation time was too short for a judgment to be made about recovery. Additional features of the recovery curve were a slight overshoot of EP amplitude occurring immediately after clip release, seen in four animals, and a plateau in the curve which was observed in nine animals just after the fast stage at a fairly constant time ($\mu = 12.7$ minutes, $SD = 4.4$) after clip release.

EP RECOVERY AND LOCAL TISSUE BLOOD FLOW

Figure 2a summarizes the table 1 data relating clip flow to the post-clip recovery status, that is, $R$ (recovery, observed or predicted, to control level) or NR (non-recovery).

The EPs which recovered were associated with higher clip flows than those associated with non-recovering EPs ($R$: $\mu = 22.58$ ml/100 gm per minute, $SD = 6.70$, $N = 6$; NR: $\mu = 8.55$ ml/100 gm per minute, $SD = 4.60$, $N = 8$), and the difference in the means is highly significant ($P < 0.001$).

Figures 2b and c summarize also the tabulated data relating EP recovery status to the local flows measured at two to five minutes ($R$: $\mu = 41.83$ ml/100 gm per minute, $SD = 20.71$, $N = 6$; NR: $\mu = 53.61$ ml/100 gm per minute, $SD = 28.70$, $N = 9$) and at 15 to 20 minutes ($R$: $\mu = 36.60$...
ml/100 gm per minute, SD = 10.90, N = 5; NR: μ = 49.17
ml/100 gm per minute, SD = 28.67, N = 9) after release of
the clip. Statistical significance of the difference between the
R and NR means could not be demonstrated in either case,
possibly due to the large variances involved, but the results
suggest an inverse relationship between post-clip flow and
final recovery status, that is, one where recovery of the EP is
linked with lower values of post-clip flow and non-recovery
with higher flow. The flows at 15 to 20 minutes post-clip
associated with the recovering EPs were significantly lower
than the control flows (μ = 52.0 ml/100 gm per minute,
SD = 7.69, N = 6) for those EPs, at the P = 0.025 level.

EP RECOVERY AND LEVEL DURING THE CLIP

The level of the EP remaining during the clip was much
higher in the animals where EP recovery was subsequently
complete (μ = 63.98% of control, SD = 36.88, N = 6) than
in the non-recovery animals (μ = 7.08% of control,
SD = 6.76, N = 9). The difference in the means is signifi-
cant at the P = 0.015 level.

EP RECOVERY AND LOCAL TISSUE Po2

Figure 3a summarizes the data of table 1 relating clip Po2
to recovery status. The clip Po2 associated with the EPs
which recovered (μ = 51.70% of control, SD = 18.00,
N = 6) was much higher than that associated with non-
recovering EPs (μ = 6.85%, SD = 7.87, N = 6). The
difference between the means is significant at the P = 0.001
level. Figure 3b shows that EP recovery was similarly
associated with much higher Po2 levels (μ = 141.08%,
SD = 60.32, N = 5) than was non-recovery (μ = 39.85%,
SD = 32.89, N = 6) when the Po2 was measured
immediately following release of the clip. The difference
in the means is significant at the P = 0.008 level. A similar
result was found in respect of Po2 measured at 15 to 20
minutes post-clip, as shown in figure 3c (R: μ = 121.92%,
SD = 33.98, N = 5; NR: μ = 69.47%, SD = 59.35, N = 6),
but the large Po2 variances generally characteristic of tissue
recordings may have precluded statistical significance for
this result.

These data demonstrate, therefore, a strong association
between recovery and relatively high post-clip Po2, but stand
in contrast to the corresponding post-clip flow data which
suggest an inverse relationship to recovery.

THE FACTOR OF DIFFERENT OCCLUSION DURATION IN
EP RECOVERY

Comparison of the two main groups of clip durations (15
to 31 minutes and 50 to 65 minutes), in respect of EP final
level, shows that the level to which the EP finally recovered
was not significantly greater in the short-occlusion group
(μ = 89.33%, SD = 25.90, N = 9) than in the long-
occlusion group (μ = 74.35%, SD = 25.64, N = 6).

SENSITIVITY OF THE EP TO CHANGES IN LOCAL TISSUE
Po2 DURING THE CLIP AND POST-CLIP PHASES

Table 2 summarizes the observations made during 23
separate periods of air-breathing (air episodes) in nine
animals. In some preparations data were available from two
separate EP recording electrodes placed on the somato-
sensory strip, each with its associated flow and Po2 elec-
trodes, so that a total of 38 observations of the effects of
the air episode was recorded. The data in table 2 have been
averaged over all electrodes for each animal in each phase.

During the air episode the recorded tissue Po2 invariably
decreased. The level of the EP, however, did not always
change; but when a change occurred, it was always a
decrease and was, with one exception, reversible upon
restoration of the pure O2 supply. Since the cortical EP is
substantially reduced from its control level and in many
cases completely abolished when the local blood flow falls
below the critical level, we could observe the effect of the
air episode on the EP in the clip phase only in the small pro-
portion of cases when some fraction of the EP remained
(table 2).

The effect of the air episode on the EP, irrespective of
tissue Po2 changes, is summarized in figure 4a for each of the
three phases. Three points should be noted. First, in the con-
trol phase, there was no significant change in the EP (mean
ep remaining = 99.65%, SD = 0.70, N = 4). Second, dur-
ing MCA occlusion, in three animals in which the clip flow
was less than the critical level of 16 ml/100 gm per minute,
the EP was significantly depressed, falling to 36.73% of the level observed just before the air-breathing episode (SD = 5.90, N = 3, P < 0.02, paired two-tailed test). In one further animal in which the clip flow was 41 ml/100 gm per minute, well above the critical level, the EP remained unchanged during the air episode. Finally, during the post-clip phase, when flows (25 to 60 ml/100 gm per minute) were closer to control levels, there were still significant (though much smaller) reductions in the EP as a result of air-breathing (mean remaining = 95.47%, SD = 5.90, N = 9, P < 0.05, paired two-tailed test). In analyzing these results, two-tailed tests were necessary since the possibility of an increase in the EP due to the air episode, however unlikely, could not logically be ruled out a priori.

Changes in tissue Po2 accompanying these changes in electrical activity during the air episode (table 2) were similar for each of the three phases, as figure 4b shows, and were not significantly different. As previously stated, arterial Po2 during the air-breathing was within the range 60 to 100 torr.

**Table 2** Effect of Air-Breathing Episode on Local Tissue Po2 and Cortical EP

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Local blood flow (ml/100 gm/min)</th>
<th>Percent of pre-episode value remaining during episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>70.0</td>
<td>49.2 100</td>
</tr>
<tr>
<td>11</td>
<td>59.0</td>
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<td>12</td>
<td>47.0</td>
<td>55.1 100</td>
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<td>13</td>
<td>55.0</td>
<td>51.7 100</td>
</tr>
<tr>
<td>9</td>
<td>4.5</td>
<td>50.0 35.7</td>
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<td>5.5</td>
<td>37.5 50.0</td>
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<td>12.5</td>
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<td>5</td>
<td>36.0</td>
<td>6.0 93.0</td>
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<tr>
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<td>60.0</td>
<td>19.2 100</td>
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<tr>
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<td>34.0</td>
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<td>9</td>
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</tr>
<tr>
<td>13</td>
<td>45.0</td>
<td>38.4 100</td>
</tr>
</tbody>
</table>

**Discussion**

When the MCA is occluded under the experimental conditions described, the degree of ischemia in a given region determines whether or not the EP is significantly depressed. Severe electrophysiological depression, often to a very small fraction of control level, occurs when the local blood flow falls below a critical level of about 16 ml/100 gm per minute, as established previously, in the present study and shown also in data derived from the monitoring of EEG and flow over wider brain areas with less localization; additional corroborative data at the level of degree of ischemia maintained, as in these experiments, for individual cortical neurons has recently been presented by Heiss et al. Our present data indicate, further, that this degree of ischemia maintained, as in these experiments, for longer than 15 minutes results in incomplete recovery of the EP in the post-clip phase, at least over the hour or so following removal of the clip. During this period the local blood flow has been restored (fig. 2), but tissue Po2 remains reduced (on average) to levels well below control (fig. 3).

On the other hand, if the critical level of ischemia is not attained, the EP is much less depressed and in the subsequent post-clip phase there is recovery of the EP together with normal flow, with a strong suggestion of tissue hyperoxia (fig. 3). These data may be interpreted as demonstrating an experimental condition similar to that termed the "luxury-perfusion syndrome" by Lassen. During EP recovery, tissue Po2 tends to be greater than normal, probably due to vasodilatation accompanied (or induced) by factors such as local metabolic acidosis, and the tissue does not appear to be able to use the abundant O2 supply immediately since functional recovery is gradual; however, the presence of this supply may be a necessary condition for ultimate complete recovery of function. The fact that throughout recovery the tissue flow is not, on average, above normal levels (fig. 2) does not necessarily contradict this interpretation. Waltz, in discussing the phenomenon of red venous blood, has pointed out that luxury perfusion may only be relative; the flows associated with hyperoxia may well be higher than elsewhere, yet lower than normal.

**The Reduced Post-clip Po2 Levels Associated with Non-recovery**

Our data show that regions of tissue rendered sufficiently ischemic to depress the EP substantially remain relatively hypoxic, even after restoration of flow, in the post-clip phase with incomplete recovery of the EP. This dissociation (of low recorded Po2 from normal recorded tissue flow) may be accounted for by one of the following two hypotheses: First, Po2 as recorded by our electrodes may appear appreciably below control levels because O2 is being consumed by the tissue at an abnormally high rate during what nevertheless proves subsequently to be an incomplete functional recovery. This seems unlikely, especially since it would imply high values of CMRO2 and therefore be inconsistent with previous results demonstrating reduced O2 consumption following hypoxic stress. Alternatively, tissue Po2 may

**Figure 4** Effect of ventilating the animal with air (instead of oxygen) on the EP (a) and on tissue Po2 (b). Each ordinate is expressed as percentage of the level present immediately prior to the air episode.
appear low because portions of the associated capillary microcirculation remain underperfused, with an effective increase in average intercapillary distance causing a corresponding impediment in diffusion of oxygen to both neuronal components and \( P_{O_2} \) electrode alike. In this situation of patchy and generally reduced capillary perfusion, the tissue flow obtained using a hydrogen electrode, however, might be affected less than the recorded tissue \( P_{O_2} \) and even appear normal (as our data in fact indicate).

The second of these hypotheses appears the more likely. Partial blockage of the vascular network can, according to Waltz, explain the known facts about red venous blood in ischemic cortex. Siesjö and Plum, in reviewing the pathophysiology of anoxic brain damage, discuss results suggesting that gross inhomogeneities of flow may follow moderate ischemia and that a high venous \( P_{O_2} \) being more heavily weighted in favor of the well-perfused areas, does not necessarily reflect the adequacy of the tissue oxygenation. Tissue acidosis, especially, may predispose the tissue to regional non-perfusion.

These considerations lead us to suggest that, in our experiments, conditions sufficient for the production of regional non-perfusion (or, at least, underperfusion) were sometimes present long enough during MCA occlusion to cause a degree of irreversible anoxic neuronal damage, preventing full recovery of the tissue \( P_{O_2} \) and EP levels in the post-clamp phase. Among these conditions was a degree of ischemia sufficient to depress the EP substantially, the flow falling below the previously discussed critical level of about 16 ml/100 gm per minute. In these cases, the damaged portion of the local neural tissue would not contribute to the EP amplitude in the post-clamp phase.

**EFFECTS OF REDUCTION IN ARTERIAL \( P_{O_2} \)**

The data on the air-breathing episodes show that when the blood flow is low enough to depress the EP, a superimposed relative hypoxemia depresses the EP still further, although a similar degree of hypoxemia has no effect on normally perfused brain. The results again are consistent with the hypothesis that under conditions of local metabolic acidosis (induced here by the ischemia) some regional non-perfusion is established so that, during the ischemic phase, a subsequent drop in \( P_{O_2} \) would tend to have a greater effect on the EP than in the normal state. In the posts ischemic phase, as our data also show, there is still a small but significant sensitivity of the EP to an equivalent hypoxic stress, presumably because the tissue is still (but less) acidotic.

These results also have clinical implications. Since the effect of air-breathing on the EP was found to be reversible, it is likely that the effect of the converse procedure (increasing the \( P_{O_2} \) from normal physiological levels) would be to reduce the depression of the EP produced by partial ischemia. We therefore are led to suggest, albeit without as yet direct experimental verification, that any vasoconstrictive effects of pure \( O_2 \) inhalation at 1 atmosphere, minor in themselves, would be outweighed by the improvements in the functional integrity of the sensorimotor cortex produced by the increased tissue \( P_{O_2} \) supply to regions affected by ischemia but still viable. If true, this would resolve the inconclusive result of Regli et al., who were unable to demonstrate consistent beneficial effects of such treatment on either CBF or the electrocorticogram, and would provide an electrophysiological basis for the validity of normobaric \( O_2 \) therapy in appropriate stress situations.

**THE QUESTION OF LONG-TERM RECOVERY FOLLOWING TEMPORARY ISCHEMIA**

Although, as stated, there was no indication of a later stage of EP recovery in addition to that already characterized by the exponential form, our constraint of a finite period of observation in the post-clamp phase in these acute preparations prevents us from stating with certainty that an EP which we judged here not to have recovered would never do so. There is evidence that posts ischemic functional deficits may be caused not by failure of the tissue energy state but by failure of the more sensitive components of neuronal mechanism (such as synaptic transmission) to recover.

Associated with, or underlying, this neuronal failure are biochemical lesions involving, for instance, a deranged state of protein synthesis which may persist in neuronal tissue following ischemia. The extent to which these factors may recover following temporary and partial ischemia, the correspondence between metabolic and electrophysiological recovery, and their relationship to neurological recovery are questions which remain to be answered, requiring in part the longer time scale of chronic experiments.

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