DURRING CEREBRAL ISCHEMIA, neuronal integrity is compromised by energy failure due to lack of metabolic substrates and oxygen. The brain is particularly sensitive to ischemic damage because its energy reserve is very low. Yet, suppression of integrated synaptic function and electrocortical activity occurs well before major depletion of energy stores. Ischemic induced defects of integrated electrocortical activity can exist after metabolic function returns to normal. The dissociation between neuronal function and cellular energy stores implies the presence of controls that decrease energy demand when energy conservation is disrupted. This means that restoration of the baseline mitochondrial state is insufficient for reestablishment of electrophysiological activity after transient ischemia, suggesting that the metabolic capability to respond to increased energy demand also is required.

This question may be of critical importance in understanding the processes that reduce cellular energy demand when the energy supply is threatened by ischemic insult as well as the limitations placed on the energy conservation system by residual defects that exist during reperfusion.

To approach this question, metabolic activity, as indicated by shifts in the reduction/oxidation ratio of cytochrome c oxidase (cytochrome a,a$\alpha$), was recorded in vivo by reflection spectrophotometry before and after transient ischemia produced by the method of Pulsinelli. Such measurements provided a direct indication of oxidative metabolic function since cytochrome a,a$\alpha$ is the final reactant with molecular oxygen in mitochondria and its redox state has been shown to signal oxygen sufficiency and respiratory chain turnover. Studies were performed during the “steady state” and during the “active” state provoked by electrical stimulation of the cortical surface. The latter allowed assessment of the effects of transient ischemia on dynamic changes that occur when mitochondria respond to increased energy demand.

We conclude that transient ischemia produces residual mitochondrial metabolic dysfunction during reperfusion and that this effect continues well beyond the time of apparent recovery of the baseline mitochondrial redox state. Electrocortical activity remains abnormal until after this residual dysfunction resolves. We speculate that this residual dysfunction results from alterations in the ability of substrate to enter the respiratory chain. A preliminary report of this work has been presented.

**Methods**

Male Wistar rats with a mean weight of 362 g (range 295-410 g) were anesthetized with sodium pentobarbital (55 mg/kg i.p.). Polyethylene cannulae were placed in the trachea, a femoral artery and a femoral vein. Systemic blood pressure was monitored with the femoral artery catheter which was also used for collection of arterial blood samples. The carotid arteries were exposed, the carotid sheaths dissected, and silk ligatures were placed about the arteries. Silastic tubing split lengthwise was used as a protective cuff about each artery to prevent direct contact by surgical clamps. The resiliency of the silastic cuff was demonstrated by tubocurare hydrochloride (10 mg/kg) and artificial ventilation which was provided with 30% oxygen, 70% nitrogen. Blood samples (150$\mu$l) from the arterial catheter were processed with a Radiometer-Copenhagen PMH Mk2
acid/base gas analyzer. Arterial blood gas and pH values were maintained within physiological limits by adjustment of the respiratory minute volume. Supplemental doses of pentobarbital (0.15 mg/kg) were given at hourly intervals through the femoral venous cannula. Body temperature was monitored with a rectal thermistor and maintained at 37°C with a heating pad.

The rat was positioned in a head holder and a midline scalp incision was extended to the level of the upper thoracic vertebrae. The paraspinal musculature was bluntly dissected from the lamina of the second cervical vertebra to reveal the alar foramen. The scalp was retracted, and a 4 mm by 6 mm craniotomy was fashioned in the right parietal bone by gradually thinning the calvarium with a low speed dental drill until the bone flap could be removed with fine forceps. Hemostasis was achieved with the aid of Gelfoam (Upjohn) gauze. The dura was left intact.

Cytochrome $a,a_t$ reduction-oxidation shifts were monitored by dual-wavelength reflection spectrophotometry. Light from 2 monochromators was alternately presented to the ends of 2 optical fiber bundles whose fibers were randomly combined into a single bundle. The light from this bundle was directed at the surface of the exposed dura. The "sample" wavelength was chosen at the peak of absorption of reduced cytochrome $a,a_t$ (605 nm). A wavelength (590 nm) "equibestic" to the "sample" wavelength for changes in Hb/HbO$_2$ was used as a reference. Scattered light returning from the cortical surface was collected with a microscope objective and detected by a photomultiplier tube housed in the microscope barrel. The working distance of the objective was 33 mm and the optical field was 3.2 mm in diameter. The difference between the light reflected during the period of illumination at 605 nm and the period of illumination at 590 nm (605-590 nm) was considered an index of the relative amount of reduced cytochrome $a,a_t$. A feedback regulation circuit was used to maintain the output of the photomultiplier constant during the reference light illumination period. This was done by varying the high voltage supply to the photomultiplier, thus varying its gain. This feedback control voltage has been shown to be a useful index of local blood volume.

A DC-coupled silver-silver chloride wire electrode was placed in the center of the optical field to record the cortical potential, and a pair of stainless steel stimulating electrodes, separated by 0.8 mm, were positioned 0.9 mm from the recording electrode with the aid of an ocular reticle. A disk reference electrode was placed under the scalp on the skull midline rostral to the craniotomy. Changes in cortical redox state were provoked by trains of 0.5 ms electrical pulses at 20 Hz lasting 2 seconds. Stimulating voltages ranged from 7 to 30 volts and were applied in a gradually increasing fashion to avoid provoking spreading cortical depression. Such stimulation resulted in cytochrome $a,a_t$ oxidations together with increases in local blood volume and negative steady potential (SP) shifts.

Eight to 14 such stimuli were given over a 10 minute period at selected times throughout the experiment. After a control series of stimuli were given, the vertebral arteries were electrocoagulated in the manner of Pulsinelli by the insertion of a cautery probe into each of the alar foramen. The animal was allowed 60 to 90 minutes to recover before a second stimulus series was performed. Predominance of carotid circulation to the cortex made ischemic injury due to vertebral coagulation unlikely. An estimate of the reducible cytochrome $a,a_t$ pool size was then determined by allowing the animal to respire 100% nitrogen for 30 seconds. Recovery without sequelae was expected after this short period of hypoxia. Thirty minutes later the carotid ligatures were tightened for 10 minutes. Cortical stimulation was performed 15, 30, 60, 120, and 180 minutes after release of the carotid ligatures. The estimate of reducible cytochrome $a,a_t$ was again determined at the end of the recovery period and compared to the final level of reduced cytochrome $a,a_t$ obtained during terminal 100% nitrogen respiration. Besides pool size estimates, these brief nitrogen induced reduction periods provided an index of comparison for ischemia induced reduction. The experimental protocol was arranged to insure that at least 30 minutes elapsed between any supplemental dose of pentobarbital and any stimulus series since phenobarbital alters the oxidative response to stimulation. No supplements were given from 30 minutes before carotid occlusion until after the stimulus series 60 minutes after clamp release.

Analysis of the response of cytochrome $a,a_t$ and relative blood volume to brain stimulation involved quantification of the evoked transients. The absolute magnitude of this oxidation ($P_{max}$), the time from stimulus onset to attainment of this peak ($t_P^{max}$), and the time from the peak to the half recovery point to the original baseline ($t_{1/2}$) were measured. Derived quantities included the ratio of peak blood volume increase to peak cytochrome $a,a_t$ oxidation (the BV:CYT ratio) and the slope of the least squares regression relating peak cytochrome $a,a_t$ oxidation to the corresponding SP shift. If the range of SP shift amplitude obtained by cortical stimulation was less than one millivolt, the least squares regression was not included in the data considered.

Amplitudes of the optical signals were based on percentages of the full scale signal. For cytochrome $a,a_t$, zero was the signal recorded when no "sample" light was available to tissue illuminated by full "reference" light. Full scale was defined when equal "sample" and "reference" signal were recorded under "resting" (unstimulated) conditions. The blood volume signal was expressed as a percent of the high voltage initially applied to the photomultiplier tube.

Results

Data were collected from 14 rats which had bilateral vertebral artery coagulation followed by a 10 minute occlusion of both carotid arteries. Arterial
blood gas values were maintained within normal limits (i.e., \( P_aO_2 \) 100 mm Hg, \( P_aCO_2 \) 35 to 40 mm Hg). Arterial blood samples taken prior to carotid occlusion gave group means of \( pH \) 7.39 ± 0.01 (±SEM), \( P_aCO_2 \) 38 ± 2 mm Hg, and \( P_aO_2 \) 119 ± 4 mm Hg. The mean systemic arterial blood pressure prior to carotid occlusion was 135 ± 4 mm Hg.

Ischemic Interval

In all rats, occlusion of both carotid arteries was followed by immediate systemic hypertension (mean pressure 195 ± 5 mm Hg). In 5 animals this hypertensive response was maintained throughout the entire ischemic interval. In 9 animals the hypertension resolved, usually beginning at the 6th or 7th minute, and systemic blood pressure returned to a mean of 112 ± 10 mm Hg just prior to release of the ligatures.

Cytochrome \( a,a_2 \) quickly became more reduced after carotid occlusion. Between 15 and 30 seconds after occlusion an inflection occurred in the data record. This point was termed the "first reduction plateau." After this point, cytochrome \( a,a_2 \) either continued to become more reduced (7 rats) or a brief period of reoxidation (7 rats) occurred. Figure 1 shows an example of transient reoxidation of cytochrome \( a,a_2 \) following the first reduction plateau during carotid occlusion.

To provide a more quantitative index of cytochrome \( a,a_2 \) reduction during carotid occlusion, comparisons were made with the level of reduction recorded during 30 seconds of respiration with 100% nitrogen and with the complete reduction obtained during terminal nitrogen respiration. In 10 of 14 rats the level of cytochrome \( a,a_2 \) reduction prior to release of carotid clamps was higher than the first reduction plateau and 98 ± 4% of the momentary reduction level achieved by 30 seconds of nitrogen respiration given prior to carotid occlusion. In 4 of 14 rats the level of reduction prior to release of carotid ligatures was equal to or lower than the first reduction plateau and 61 ± 14% of the 30 second reduction level. There was no correlation between the occurrence of sustained or transient systemic hypertension during carotid occlusion and the level of cytochrome \( a,a_2 \) reduction prior to carotid ligature release (chi-square corrected: \( p = 0.92 \)). For comparison, the momentary reduction level achieved by 30 seconds of nitrogen respiration given at the end of the experiment was 86 ± 7% of the "complete" reduction level that occurred during terminal nitrogen respiration.

Electrocortical activity was abolished within 30 seconds of carotid occlusion in all rats. In 3 some low voltage activity returned after 2 to 4 minutes and disappeared again after lasting from 1 to 4 minutes. Two of these were from the group of 4 animals with the lower degree of cytochrome \( a,a_2 \) reduction prior to reperfusion. Electro cortical activity remained isoelectric throughout the period of carotid occlusion in all other rats. Electrical seizure activity, defined as spike-wave discharges or bursts of high amplitude sharp waves, was not seen during the occlusion or reperfusion period.

**Figure 1.** Changes occurring during and following 10 minutes of cortical ischemia produced by vertebral coagulation followed by reversible carotid ligation in the rat. During ischemia the amount of reduced cytochrome \( a,a_2 \) is increased. After an initial inflection in the optical record, the amount of reduced cytochrome \( a,a_2 \) continues to increase until carotid ligature release. The early reperfusion period is characterized by hyperoxidation of cytochrome \( a,a_2 \) beyond control levels with eventual return to the resting state. Local blood volume is indicated by cortical light absorption at 590 nm. S.A.P. signifies systemic arterial blood pressure.
Cortical absorption at 590 nm ("blood volume") showed a biphasic response during carotid occlusion. During the first 30 seconds, absorption at 590 nm decreased, but then returned to a level above its starting point. In 6 rats it remained at this elevated level, in 8 it gradually decreased to a point at or below the initial level by the time of ligature release.

**Period of Reperfusion**

The systemic blood pressure decreased immediately upon release of carotid ligatures. In the 5 animals with elevated blood pressure prior to ligature release, it returned to near the preocclusion level. If the blood pressure had not been elevated at the time of ligature release (9 rats), it dropped into a hypotensive range (69 ± 5 mm Hg). In all animals blood pressure returned to the preocclusion range within 15 minutes of reperfusion.

The level of reduced cytochrome \( a_\alpha \) also dropped after reperfusion. In most rats (12 of 14) this oxidative response was precipitous. In all, the level of reduction fell below the preischemic baseline. This hyperoxidized state of cytochrome \( a_\alpha \) was transient, reaching its peak at 7 ± 1 minutes. The cytochrome redox state was restored to the pre-ischemic baseline in 16 ± 3 minutes. Cortical absorption at 590 nm increased upon reperfusion.

Electrocortical activity returned gradually during reperfusion. Within 15 minutes some low voltage slow and occasional sharp activity were seen. At 60 minutes faster frequencies had returned while the voltage remained depressed. At 180 minutes the activity was nearly normal to visual inspection with some intermittent slowing remaining. This pattern is seen in figure 2.

**Response to Cortical Stimulation**

To test the ability of the metabolic system to respond to increased energy demand after transient ischemia, trains of electrical pulses of varying voltage were applied to the cortical surface. Such stimulation produced a graded response in the magnitude of the negative steady potential shift. Figure 3 demonstrates the oxidation of cytochrome \( a_\alpha \) (CYT Pmax) and transient increase of blood volume (Bl. Vol. Pmax) that also accompany such stimulation. The magnitudes of these changes were correlated with the magnitudes of the SP shifts (filled circles, fig. 4). The intercept of the cytochrome \( a_\alpha \) regression line was positive but not significantly different from zero (2 tailed t-test, \( p = 0.44 \)). The time to peak cytochrome \( a_\alpha \) oxidation (tPmax) and half-recovery (1/2 off) were not strongly correlated with the magnitude of the oxidation (filled circles, fig. 5). A similar situation existed for the times to peak blood volume onset and half-recovery.

Stimulus series were performed before and after vertebral artery coagulation prior to carotid occlusion. As seen in the table, vertebral coagulation did not produce a significant change in any of the parameters used to describe the transient metabolic and blood volume response to cortical stimulation.

**Effect of Carotid Occlusion**

Of 14 rats subjected to transient carotid occlusion, 11 showed decreased peak oxidation of cytochrome \( a_\alpha \) produced by cortical stimulation after release of the carotid ligatures. Of these, 8 showed recovery of cytochrome \( a_\alpha \) oxidative transient amplitude within the 3 hour reperfusion period. Three rats showed sup-
Control METABOLIC DYSFUNCTION AFTER TI/Duckrow et al.

FIGURE 3. Responses of local cortical blood volume (upper traces), cytochrome $a,a_s$ redox state (middle traces), and steady potential (lower traces) to electrical stimulation. Responses before carotid ligation (control) and 3 hours after ligature release (180 min) are similar. In the early reperfusion period (15 min) the amplitude of the cytochrome $a,a_s$ response (middle trace) is decreased despite a larger SP shift. The time to half recovery is prolonged. This lengthening of recovery time is shown more clearly by normalizing the response amplitude of the cytochrome $a,a_s$ responses as shown at the bottom right (solid line = control, dotted line = 15 min of reperfusion, dashed line = 180 min of reperfusion). The blood volume traces have been scaled to their respective cytochrome $a,a_s$ responses.

pression of peak evoked oxidation without recovery after 3 hours of reperfusion. Three rats did not show suppression of evoked cytochrome $a,a_s$ oxidation at any time, and these were in the previously mentioned group of 4 having a level of reduced cytochrome $a,a_s$ at the end of the carotid occlusion interval less than the “first reduction plateau.”

The reducible cytochrome $a,a_s$, determined by 30 seconds of nitrogen respiration at the end of the experiment, averaged $91 \pm 6\%$ of the reducible cytochrome $a,a_s$ determined by the same method prior to carotid ligation for the 11 animals that either showed no suppression of the transient cytochrome $a,a_s$ response or showed suppression with recovery. In the

FIGURE 4. Relationships between the magnitude of cytochrome $a,a_s$ oxidation, blood volume increase, and steady potential shift (SP shift) evoked by direct cortical stimulation of varying intensity. These data points represent responses to cortical stimulation in a single animal. Open circles represent data taken 15 minutes after removal of carotid ligatures. Filled circles are control data, and squares represent data recorded after 180 minutes of reperfusion.
3 animals that showed suppression of the transient cytochrome \( a_5 \) response without recovery the reducible cytochrome \( a_5 \) at the end of the experiment was 63 ± 11% of the same pool prior to carotid occlusion. The difference between these 2 groups was not significant (\( p = 0.06 \)).

Data from one of the 8 rats that showed suppression and recovery of the peak oxidative response after transient ischemia is shown in figure 4. The slope of the linear relation between peak cytochrome \( a_5 \) oxidation and SP shift was decreased 15 minutes after release of the carotid ligatures. The amplitude of the corresponding blood volume increase was unchanged. The intercept of the cytochrome \( a_5 \) regression line increased to a value significantly greater than zero (\( p = 0.03 \)). After 180 minutes of reperfusion these values were returning to control levels. The group means for the relationship of the peak cytochrome \( a_5 \) oxidation to the peak SP shift during the reperfusion period are shown in figure 6 (\( \Delta C Y T P_{\text{max}}/\Delta S P \) Shift). Suppression of the response was seen 15 and 30 min after reperfusion.

The time required for cytochrome \( a_5 \), transiently oxidized after stimulation, to become re-reduced to half the baseline reduction/oxidation ratio (\( t_{1/2} \) off) was lengthened during the early reperfusion period. This is shown for individual rats in figures 3 and 5. The group means in figure 6 show this lengthening (doubling) persisted for 2 hours after release of the carotid ligatures and returned to the control level after 3 hours of reperfusion.

Mean values of descriptive indices for metabolic

![Figure 5](image-url)

**Figure 5.** Relationship between the \( t_{\text{Pmax}} \) and \( t_{1/2} \) off and the amplitude of the vascular or metabolic responses. These data points represent responses to cortical stimulation in a single animal. Open circles represent data taken 15 minutes after removal of carotid ligatures. Filled circles are control data, and squares represent data recorded after 180 minutes of reperfusion.

**Table** Stimulus Series - Vertebral Coagulation Produced No Significant Change in Transient Metabolic and Blood Volume Response to Cortical Stimulation

<table>
<thead>
<tr>
<th></th>
<th>Cyt. ( t_{\text{Pmax}} )</th>
<th>Cyt. ( t_{1/2} ) off</th>
<th>Bl. Vol. ( t_{\text{Pmax}} )</th>
<th>Bl. Vol. ( t_{1/2} ) off</th>
<th>BV/CYT ratio</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6.4 ± 0.3 (12)</td>
<td>6.3 ± 0.6 (12)</td>
<td>5.1 ± 0.3 (12)</td>
<td>4.4 ± 0.4 (12)</td>
<td>0.088 ± 0.006 (12)</td>
<td>1.24 ± 0.18 (11)</td>
</tr>
<tr>
<td>After</td>
<td>6.8 ± 0.3 (14)</td>
<td>6.5 ± 0.7 (14)</td>
<td>5.0 ± 0.2 (14)</td>
<td>4.0 ± 0.3 (14)</td>
<td>0.084 ± 0.008 (14)</td>
<td>1.04 ± 0.19 (13)</td>
</tr>
<tr>
<td>Coagulation</td>
<td>6.8 ± 0.3 (14)</td>
<td>6.5 ± 0.7 (14)</td>
<td>5.0 ± 0.2 (14)</td>
<td>4.0 ± 0.3 (14)</td>
<td>0.084 ± 0.008 (14)</td>
<td>1.04 ± 0.19 (13)</td>
</tr>
<tr>
<td>Units</td>
<td>seconds (N)</td>
<td>seconds</td>
<td>seconds</td>
<td>seconds</td>
<td>%s / mV</td>
<td></td>
</tr>
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and blood volume transients across the group of 8 animals provide a summary of the effects of the carotid clamping and the recovery that occurred over the 3 hour observation period (fig. 6). There was a 14% increase in the cytochrome a,a₃ tPmax at 15 minutes of reperfusion. There was also a 50% increase in the blood volume t½ off after 15 minutes of reperfusion. There was suppression of peak cytochrome a,a₃ oxidation for a given SP shift to 30% of control value at 15 minutes of reperfusion. This, in large part, accounts for the near doubling of the BV:CYT ratio (refer to Methods) at that time as well.

Discussion

Vertebral artery coagulation followed by carotid artery ligation produced increased reduction of cerebral cytochrome a,a₃ and suppression of electrocortical activity. Reperfusion was characterized by a period of hyperoxidation of cytochrome a,a₃. A period of continuing metabolic dysfunction intervened between reestablishment of the baseline redox state and return of baseline electrocortical activity. This dysfunction was characterized by decreased amplitude of the transient oxidative response of cytochrome a,a₃ to increased cortical work induced by direct cortical stimulation. The time required for cytochrome a,a₃ re-reduction after stimulus induced oxidation was prolonged. This prolongation suggests relative substrate limitation was induced by ischemia and became manifest only when the quiescent brain was stimulated to perform additional metabolic "work" during the recovery period.

Increased reduction/oxidation ratios of electron transport chain components have been shown to occur during ischemia induced by various methods. Increased reductive responses are expected because the respiratory chain components of mitochondria in vitro become reduced when oxygen is limited. The degree of reduction of respiratory chain components during ischemia provides a criterion for completeness of ischemia when it is compared to the presumably complete reduction achieved during terminal nitrogen respiration. Using this criterion, vertebral coagulation followed by reversible carotid ligation did not produce complete cerebral ischemia in rat since cytochrome a,a₃ reduction did not attain the level recorded after death. Also, continuing reduction of cytochrome a,a₃ during vessel occlusion demonstrates that some oxygen remained available. Nevertheless, since electrocortical activity was suppressed, energy provision was disturbed during the ischemic interval.

Cortical reflectance at 590 nm was used as a correction for changes in hemoglobin volume and oxygenation as well as non-specific changes in light absorption and scattering by the tissue. During the
metabolic response to direct cortical stimulation this correction signal is an indicator of relative cortical blood volume. This is possible because cortical stimulation produces few non-specific changes such as alterations in brain volume or shifts of cellular water. During carotid ligation after vertebral coagulation, the surface of the brain moves and cellular water shifts are expected. For this reason, care must be taken when interpreting changes in the reference signal as changes in relative cortical blood volume.

Reperfusion after a 10 minute ischemia produced hyperoxidation followed by return of the redox state of cytochrome a,a, to the control level. Interpretation of these findings requires that the total pool of cytochrome a,a, remain unchanged, and there is evidence from liver and brain that ischemia might change this pool size. However, those rats with reversible abnormalities of metabolic response to cortical stimulation showed no decrease of the labile (reducible) cytochrome a,a, pool at the end of the 3 hour reperfusion interval. This suggests that, in those rats, transient ischemia had no permanent effect on cytochrome a,a, pool size, and the decreased absorption of light at 605 nm immediately after ligature release did, in fact, signal hyperoxidation. Such hyperoxidation has been observed after ischemia produced in a variety of models.

The rapid return of the redox state of cytochrome a,a, from the hyperoxidized condition to the baseline state was consistent with biochemical data showing rapid return of other indexes of metabolic function, including adenylyl energy charge, phosphocreatine concentration, lactate concentration and the lactate/pyruvate ratio. Electro cortical activity remained abnormal, however, suggesting decreased energy demand persisted. To determine if metabolic dysfunction persisted during this period, the brain was stimulated to increased activity by the delivery of electrical pulses to the cortical surface. Such stimulation has been shown to be associated with increases in extracellular potassium and accompanied by transient oxidation of mitochondrial NADH and cytochrome a,a, analogous to the state-4 to 3 transition of isolated mitochondria.

Cytochrome a,a, oxidations produced by cortical stimulation during reperfusion were decreased in amplitude and slowed in time course. These changes could be explained by 5 possibilities: 1) uncoupling of oxidative phosphorylation, 2) loss of mitochondrial enzymatic pool size, 3) loss of Na⁺ — K⁺ ATPase activity, 4) relative substrate deficiency, or 5) increased tissue oxygenation.

Uncoupling of oxidative phosphorylation does not appear to be a likely explanation. If uncoupling were present, increased ADP availability would cause an overall oxidation of cytochrome a,a, and increase the magnitude of oxidative responses to stimulation. During reperfusion after 10 minutes of ischemia there was hyperoxidation of cytochrome a,a, however, the magnitude of the oxidative response to stimulation was suppressed. Also, the time courses of these changes were different (cf. figs. 1 and 6).

The function of neuronal enzyme systems involved in the regulation of cellular metabolism can be compromised by anoxic/ischemic insults. This includes decreases in cytochrome a,a, pool size and Na⁺ — K⁺ ATPase activity. If the cytochrome a,a, pool size was changed by ischemia, decreasing reduced and oxidized fractions proportionately, the magnitude of any transient signal change would decrease without a change in the resting redox ratio. This could explain the decreased magnitude of the evoked oxidative transient. This is supported by data from 3 animals that did not show recovery of evoked oxidative transient magnitude and also showed a decrease of labile (reducible) cytochrome a,a,. The small size of this group precludes the establishment of statistical significance to this finding.

If the activity of Na⁺ — K⁺ ATPase were decreased by the ischemic insult, as has been reported in other preparations, one would see a ouabain-like effect. Ouaibain has been shown to slow the transient oxidation of NADH induced by cortical stimulation without affecting the re-reduction rate. Cytochrome a,a, would be expected to change similarly. The 1Pmax increased by 14% at 15 minutes of reperfusion in this experiment but was not otherwise significantly different from control (fig. 6).

Substrate deficiency could result in inappropriate oxidation of respiratory chain components due to a "state-2 like" condition. Re-reduction of cytochrome a,a, from the oxidized "active" state to the original steady state could result from increased reducing equivalent availability to the respiratory chain. Likewise, a block in reducing equivalent availability could delay re-reduction of oxidized electron transport enzymes, including cytochrome a,a,. A drop of NADH below control levels occurs during reperfusion after transient ischemia in various preparations. This suggests a substrate block despite increased 2-deoxyglucose phosphorylation early during reperfusion after transient ischemia. We attribute delayed re-reduction of the oxidative metabolic transient to a relative substrate deficiency resulting from a block of reducing equivalent flow to the electron transport chain. This block would have to exist after the phosphorylation of glucose and before the major source of NADH, the tri-carboxylic acid cycle.

Transient prolongation of recovery time has been shown to occur after intravenous phenobarbital injection. This prolongation abates after 30 minutes in cat preparations. Because phenobarbital administered as an anesthetic to the rat could cause an artifactual prolongation of the recovery time (1/2 off), doses were given hourly at least 30 minutes before cortical stimulation. Cumulative effect of the drug was unlikely since the recovery time (1/2 off) returned to baseline levels at the end of the 3 hour reperfusion period.

Vascular control of tissue oxygenation may be affected by transient ischemia, and ischemic damage to cortical vasoregulation may account for changes in steady state and dynamic metabolic activity. Oxygen delivery to cortical tissue beyond immediate metabolic
needs could cause hyperoxidation of mitochondrial respiratory enzymes. As the terminal member of the chain, and direct reactant with molecular oxygen, cytochrome \( a_a \) would be expected to be sensitive to tissue oxygen delivery. It is likely that reflex hyperemia occurring after transient ischemia,\(^{20} \) \(^{21} \) and indicated by increasing blood volume in these experiments, plays a role in the hyperoxidation of cytochrome \( a_a \) seen during the first 15 to 30 minutes. Vascular control of tissue oxygenation during periods of increased neuronal “work” may also be affected by transient ischemia. The ratio of the peak increase in cortical blood volume to the peak oxidation of cytochrome \( a_a \) induced by transient cortical stimulation increased after ischemia (fig. 6). However, this increase was primarily due to decreased evoked cytochrome \( a_a \) oxidation (seen in figs. 3 and 4). Also, prolongation of the recovery time of increased blood volume induced by cortical stimulation occurred 15 minutes into the reperfusion period. However, this indicates a possible increase in tissue oxygen delivery, perhaps sufficient to prolong the period of transient cytochrome \( a_a \) oxidation, returned to control levels 30 minutes into the reperfusion period, while prolonged oxidation of cytochrome \( a_a \) continued for 2 hours (fig. 6). These factors suggest that abnormalities of metabolic response to increased cortical “work” seen after ischemia cannot be explained completely by changes in tissue oxygen delivery.

This study demonstrates that spontaneous electrocortical activity suppressed by transient ischemia will show residual abnormalities of frequency and voltage for as long as 2 to 3 hours after reperfusion despite the return of the basal redox state of cytochrome \( a_a \). The reperfused cortex remains excitable to cortical stimulation, however, a residual lesion of energy metabolism becomes manifest when the cortex is called upon to provide for this increase in brain “work.” Transient oxidations of cytochrome \( a_a \) induced by cortical stimulation have decreased amplitude and prolonged re-reduction times for up to 2 hours after a 10 minute period of ischemia. These data are consistent with the presence of a relative block in reducing equivalent flow to the respiratory chain. After 2 hours of reperfusion the metabolic response to transient stimulation regains its pre-ischemic qualities and near-normal electrocortical activity returns. This suggests complete return of electrophysiologic activity after transient ischemia may require the resolution of metabolic defects that are manifested, not in the steady state balance of reducing equivalent flow, but, in an inability of the mechanism of energy conservation to respond to transient increases in metabolic demand.

Acknowledgment

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A Case for Cerebral Thromboangiitis Obliterans

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SUMMARY The existence of cerebral thromboangiitis obliterans (CTAO) has been controversial. The clinical, laboratory and angiographic features of a young woman with recurrent thrombophlebitis, digital gangrene and a bilateral anterior opercular syndrome (Foix-Chavany-Marie) are reported. The cerebral angiogram demonstrated significant narrowing of fronto-opercular branches of both middle cerebral arteries. Histology of small digital muscular arteries revealed segmental adventitial fibrosis, narrowing or occlusion of lumen and mild lymphocytic infiltrates; occasional veins showed phlebitis. An etiologic relationship between cerebral occlusive disease and peripheral thromboangiitis obliterans (TAO) is suggested.

IN 1879, Von Winiwarter published an account of angiopathy in a 57-year-old man with foot gangrene; he named the angiopathy endarteritis obliterans. Buerger, in 1908, designated the condition thromboangiitis obliterans (TAO). Spatz, and Spatz and Lindenberg, in 1939, published comprehensive accounts of the cerebral form of TAO (CTAO) distinguishing 2 types according to distribution of the lesions. There is a controversy in recent literature---on whether TAO and CTAO are distinct clinicopathologic entities.

A young woman affected by recurrent thrombophlebitis, digital gangrene and a Foix-Chavany-Marie (biopercular) syndrome is reported as representative of the association between cerebral and peripheral TAO. These observations buttress the present trend in angiology to consider TAO and CTAO as distinctive but rare entities.

Patient History

MOC, a 33-year-old black woman, was admitted to the hospital on August 31, 1980, because of sudden inability to talk and swallow. She had been in good health until 1966 when she had a thrombophlebitis in her left leg. One year later she developed a similar episode. In 1968 she had a right deep vein thrombosis. In 1973, at the age of 26, she suddenly had left hemiparesis. Radionuclide brain scan at the time showed increased uptake over the right parietal region consistent with an area of infarction. Bilateral carotid angiography revealed mild segmental narrowing of several of the left operculofrontal branches and an area of “luxury perfusion” over the right parietal frontal region. Routine blood tests and CSF examination were normal. Electrocardiogram and echocardiogram were normal. Electroencephalogram showed mild slowing over the left hemisphere. During the ensuing weeks she gradually recovered from her hemiparesis. During the next year she had numerous episodes of pain in her fingers and toes aggravated by cold weather and/or water. A selective left brachial angiogram revealed multiple occlusions and no opacification of the interdigital arteries (fig. 1A). A femoral angiogram was unremarkable down to the level of the ankle but failed to visualize any vessel beyond that area. Due to recurrent episodes of painful digital ischemia, she required a right transmetatarsal amputation of the left ring, right index finger, left fourth toe, and left big toe. Histologic examination of the amputated digits revealed segmental involvement of small muscular arteries several of which showed narrowing or occlusion of lumen (fig. 1B) mainly due to intimal hyperplasia and sparse mononuclear infiltration. No evidence of atheroma or calcification was seen in these vessels. None of these arteries showed fresh thromboses or vasculitis with fibrinoid necrosis. Occasional veins showed phlebitis. Focally involved vessels were surrounded by concentric layers of increased connective tissue.

In November, 1979 she had a bilateral lumbar sym-
Disparate recovery of resting and stimulated oxidative metabolism following transient ischemia.
R B Duckrow, J S LaManna and M Rosenthal

doi: 10.1161/01.STR.12.5.677

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