CORTICAL REDOX STATE AND BLOOD FLOW/Ginsberg et al.


Pyridine Nucleotide Redox State and Blood Flow of the Cerebral Cortex Following Middle Cerebral Artery Occlusion in the Cat

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SUMMARY Acute changes in the redox state of NADH in the cerebral cortex of cats were investigated following occlusion of the middle cerebral artery (MCA) and were correlated with alterations of regional cerebral blood flow in the ischemic cortex determined autoradiographically. Arterial occlusion was accomplished via the transorbital approach. Cortical fluorescence and reflected light signals were recorded from the central MCA territory by means of a beam-splitting fluorometer, and a fluorescence signal corrected for alterations in intravascular hemoglobin was derived. Following arterial occlusion, there was a rapid increase in cortical NADH fluorescence, peaking within 30 to 70 seconds at 20% to 40% of full scale. This was followed by a slow linear decline in fluorescence over the next several minutes. The behavior of cortical NADH fluorescence was unaffected by replacement of the ambient air over the cortical surface with nitrogen. Mean regional blood flow values in the most ischemic gyri two to 15 minutes following arterial occlusion were 21% to 23% of the corresponding values in the opposite, nonischemic hemisphere. In individual animals, peak NADH fluorescence values following arterial occlusion correlated with the extent of blood flow reduction in the affected ischemic gyri (P < 0.05).

THE EARLY BIOCHEMICAL EVENTS associated with evolving cerebral infarction are imperfectly understood. Previous experimental studies have documented changes in cerebral energy metabolites during acute focal cerebral ischemia, but alterations of the redox state of cerebral tissue under these conditions have only recently been investigated.

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It is possible to measure continuous changes in the redox state of pyridine nucleotides (PN) of the cerebral cortex in vivo owing to the property of the reduced form of pyridine nucleotides of emitting fluorescent light when appropriately excited. In brain tissue PN fluorescence is largely accounted for by reduced nicotinamide adenine dinucleotide (NADH, DPNH). Although reduced nicotinamide adenine dinucleotide phosphate (NADPH, TPNH) accounts for a considerable proportion of PN fluorescence in certain nonnervous tissues, its contribution to the fluorescence of brain tissue relative to that of NADH is negligible. Previous studies in a variety of tissues including brain have established the similarity of the fluorescence emission spectrum of tissue and that of pure NADH (see for review). Chance et al. and Jöbbsis et al. have shown a correlation...
between the directly assayed PN content of cerebral cortex and fluorescence measurements.

In this study, we have examined changes in the redox state of the cerebral cortex of cats during acute focal cerebral ischemia produced by middle cerebral artery (MCA) occlusion and have correlated local redox changes with alterations of regional cerebral blood flow (rCBF).

Methods

ANIMAL PREPARATION

Cats of either sex, weighing 2.2 to 4.1 kg, were anesthetized with intraperitoneal sodium pentobarbital, 40 mg per kilogram. In some animals supplemental doses of 10 mg per kilogram were required to maintain surgical anesthesia. Polyethylene catheters were introduced into one femoral artery and vein. A #24 Teflon catheter was placed in the other femoral artery to permit sampling during the subsequent antipyrine studies. The right lingual artery was cannulated in a retrograde manner with a PE 50 catheter. A tracheal cannula was introduced. Animals were then paralyzed with intravenous gallamine triethiodide, 10 mg initially and 3 to 5 mg at intervals of 30 to 60 minutes thereafter. They were ventilated with a Harvard respirator on a mixture of 30% oxygen and 70% nitrogen.

Arterial blood pressure and end-tidal carbon dioxide content were monitored with a Hewlett-Packard transducer and a Beckman infrared CO2 analyzer, respectively, and were recorded on the channels of a polygraph (Hewlett-Packard). Rectal temperature was maintained at 37°C by a thermostatically controlled infrared lamp.

The head was then secured in a headholder and the right MCA exposed via a transorbital dissection. The approach of O'Brien and Waltz11 was modified for use in these acute experiments to permit a wider exposure. The origin of the temporalis muscle was detached and the bone surrounding the optic foramen removed to expose an 8 to 10-mm ellipse of dura overlying the optic nerve. The dura was gently removed without trauma to the underlying brain. The brain surface was kept moist with warm saline. In several animals, a bipolar EEG was recorded from each hemisphere via brass screw electrodes placed anteriorly and posteriorly to the burr hole on the right and in corresponding locations on the left.

Pyridine nucleotide fluorescence was recorded from a portion of the exposed brain surface with a fluorometer designed by Chance and Legallais12 and modified by Jöbsis et al.10 The instrument employs a 1,000-watt water-cooled high pressure mercury arc (Philips SP950W) operated by an AC power supply. A Corning 5874 primary glass filter and an infrared light-absorbing glass filter permit the passage of an ultraviolet band peaking at 366 nm. The objective lens system is a Leitz Ultropak 6X with a dipping cone, which makes light contact with the brain surface. A monocular eyepiece (6X) permits the system to be focused precisely on the field, which is approximately 2.8 mm in diameter. A prism splits the light returning from the field in a ratio of 6 to 1, the former portion being analyzed for fluorescent light at 445 nm by means of an interference filter and a Kodak Wratten 2A filter. The latter portion is analyzed for reflected light at 366 nm by two Corning 5874 filters. EMI photo-multiplier tubes (9524B, 9592B) detect fluorescent and reflected light signals which are buffered and fed to a sample and hold stage, where they are synchronously demodulated. The signals are also displayed on a Hewlett-Packard polygraph. Output signals of 0.5 volt are set equal to full scale, and subsequent changes in fluorescence or reflectance are expressed as percentages of full scale. A more detailed account of the instrumentation employed is presented elsewhere.6

Preliminary Studies

In order to assess the extent of the perfusion deficit following MCA occlusion, the right MCA was occluded by bipolar coagulation. Thirty minutes later, the thorax was opened via a median sternotomy incision, the pericardium was incised, and a plastic cannula was introduced through the left ventricle into the root of the aorta, where it was securely ligated. The descending aorta was occluded distal to the left subclavian artery to prevent perfusion of the lower body. Carbon black suspension (20 cc) (Pelikan, Guenther Wagner, Germany) was perfused through the aortic cannula under a pulsatile pressure head averaging 100 mm Hg. The brain was removed, immersed in 10% formaldehyde solution, and examined grossly.

Figure 1: Brain of a cat perfused with a colloidal carbon suspension 30 minutes following occlusion of the right MCA. Circle denotes area within which the optical field for fluorometry was selected. PE = posterior ectosylvian gyrus, ME = middle ectosylvian gyrus, PS = posterior sylvian gyrus.
In order to correct for fluorescence artifacts produced by fluctuations in intravascular hemoglobin concentration, use was made of a calibration technique in which the hemoglobin concentration is intentionally perturbed.\(^6\)\(^-\)\(^13\) Prior to MCA occlusion, small pulses of saline (0.5 to 1.0 ml) were injected over one second into the right carotid circulation via the lingual artery catheter. These result in only momentary changes in hemoglobin concentration in the field under observation and hence are insufficient to produce tissue hypoxia. The focal hemodilution leads to a transient positive excursion in the measured fluorescence and reflected light signals. Prior studies have shown that under defined experimental conditions, a saline flush causes a constant ratio of peak intensity shifts in the fluorescence versus reflected light signals.\(^*\) Accordingly, this ratio, k, may be used to calculate the "corrected" fluorescence value by means of the expression:

\[ F_c = F_u - k \cdot R \]

where \( F_c \), \( F_u \), and \( R \) represent the magnitude of change of the corrected fluorescence, measured (uncorrected) fluorescence, and reflected light signals, respectively. \( F_c \) thus represents that portion of the measured fluorescence signal due to emitted cortical fluorescence (i.e., independent of hemodilution phenomena).

Corrected fluorescence was also obtained electronically by inverting and algebraically summing the reflected light signal with the measured fluorescence signal; the corrected fluorescence signal was displayed on the polygraph and was electronically balanced so as to exhibit zero deflection during saline flushes of the lingual artery performed prior to vascular occlusion.

**REGIONAL CEREBRAL BLOOD FLOW**

In the majority of animals used for fluorescence studies, determination of rCBF was made by means of an autoradiographic technique employing \(^{14}C\)-antipyrine. The method of Reivich et al.\(^14\) was employed, with the following modification: during the antipyrine infusion, arterial samples were collected at five-second intervals from the tip of the \#24 Teflon catheter, which was allowed to flow freely. The short length (16 cm) and small diameter of this catheter permit a flow rate sufficient to clear the catheter volume several times between each sample, thus obviating the need for a catheter smearing correction. The samples were then quantitatively pipetted onto whatman \#2 paper and counted in the usual manner. Autoradiograms were prepared from 20 micra frozen sections made at 1-mm intervals through the central two-thirds of the cerebral hemispheres. Multiple densitometric measurements were carried out on the individual gyri known from the preliminary study to fall within or adjacent to the territory of the MCA; measurements were also made of the central white matter and of areas of thalamus.

**Results**

**PERFUSION STUDY**

Three animals were perfused with carbon black suspensions 30 minutes following right MCA occlusion. Surface examination of all brains revealed a striking perfusion defect involving the right posterior sylvian, middle ectosylvian, and posterior ectosylvian gyri (fig. 1).\(^14\) The zone of hypoperfusion extended as well to involve the surrounding gyri (anterior ectosylvian, middle suprasylvian, and posterior suprasylvian), although these latter zones were less severely and more inconstantly affected. Thus, in subsequent animals, fluorescence measurements were carried out on the right middle ectosylvian or posterior ectosylvian gyri, which appeared from the preliminary perfusion study to be most hypoperfused (fig. 1).

**PHYSIOLOGICAL STATE**

The arterial blood pressure in animals with uncomplicated operative preparation averaged 158 mm Hg systolic (range 130 to 200) and 120 mm Hg diastolic (range 85 to 145) prior to MCA occlusion and remained unchanged following the occlusion. One animal was transiently hypotensive during the initial preparatory stages but subsequently maintained a normal blood pressure. A second animal, in which excessive bleeding occurred during surgical dissection, was hypotensive with a mean blood pressure below 100 mm Hg for 15 minutes, necessitating transfusion with low molecular weight dextran to restore mean blood pressure to normal (125 to 135 mm Hg). The fluorescence data of these latter animals will be considered separately.

Arterial blood gas data in the control state and at one to nine minutes following MCA occlusion are presented in table 1. No significant alteration occurred following MCA clipping.

The EEG prior to MCA occlusion contained predominantly five to seven per second activity of moderate amplitude. Within 10 to 15 seconds of vascular occlusion, there was a moderate reduction of EEG amplitude over the affected hemisphere and a slowing of the predominant frequency to three to five per second. Intermittent higher amplitude, one to two per second, slow activity was occasionally observed. These changes persisted throughout the period of occlusion.

**FLUORESCENCE DATA**

Cortical fluorescence and reflected light tracings in the control state were stable over a 20 to 30-minute period preceding MCA occlusion. Upon MCA clipping, there was an immediate increase in cortical reflected light and in the uncorrected cortical fluorescence tracing, although the previously calibrated corrected fluorescence signal remained unchanged for the first 3 to 3.5 seconds (fig. 2). This indicated that the initial increase in uncorrected fluorescence was due to an acute hemodynamic change produced by sudden vascular occlusion. Corrected cortical fluorescence

<table>
<thead>
<tr>
<th>pH</th>
<th>PO2 (mm Hg)</th>
<th>PCO2 (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td>Prior to MCA</td>
<td>7.262 ± 0.023</td>
<td>127 ± 3</td>
</tr>
<tr>
<td>Following MCA</td>
<td>7.261 ± 0.018</td>
<td>126 ± 3</td>
</tr>
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first rose at 3 to 3.5 seconds, attaining a maximum value 30 to 70 seconds following occlusion, although the magnitude of peak corrected cortical fluorescence change varied considerably among animals. Peak corrected fluorescence values ranged from 20% to 40% in those animals with an uneventful operative preparation. One additional animal, in which vascular occlusion may have been incomplete, attained a PN fluorescence rise of 6%. In the two animals with intraoperative hypotension and/or blood loss, peak fluorescence change was 27% and 68%. Figure 3 presents the mean corrected cortical fluorescence change during the first three minutes following MCA occlusion in the normotensive animals.

Following the initial peak in fluorescence, there occurred a subsequent slower decline during the next several minutes. The mean rate of decline of fluorescence (± SEM) was 0.072 (±0.015)% per second for the animals with uneventful operative preparation. In the two animals with hypotension and/or blood loss, the rate of decline tended to be less pronounced (0.03% and 0.0% per second). Among the animals in the former group which displayed a fluorescence decline, the half-times of decline as determined from semilogarithmic plots averaged 191 seconds (range 78 to 320).

The ability to record cortical fluorescence following MCA occlusion was limited by the tendency of the ischemic brain to retract slightly from the dipping cone of the objective lens system. This was signaled by an abrupt discontinuity in all channels, occurring three to five minutes following MCA occlusion. Further assessment of the fluorescence level relative to the pre-occlusion baseline would have required refocusing the fluorometer and repetition of the saline-flush calibration procedure. Inasmuch as the latter was impossible following arterial occlusion, further recording thus could not be carried out.

### Regional Cerebral Blood Flow

Mean values for rCBF determined at periods of two to 15 minutes following MCA occlusion are presented in table 2 for representative areas of the ischemic and nonischemic hemispheres in the normotensive animal group. The most pronounced decrement in rCBF produced by vascular occlusion occurred in the middle and posterior ectosylvian gyri, where rCBF was reduced on the average to 23% and 21%, respectively, of the values in the opposite hemisphere. rCBF reduction in the posterior sylvian and middle suprasylvian gyri of the ischemic hemisphere was nearly as great (table 2). Other gyri were less affected by vascular occlusion. rCBF in the central white matter was considerably reduced in the

| Table 2 Regional Cerebral Blood Flow in Representative Areas of Nonischemic and Ischemic Hemisphere (Mean of Eight Animals* = SEM, ml gm⁻¹ min⁻¹) |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Nonischemic hemisphere | Ischemic hemisphere | Ratio of CBF in corresponding regions (ischemic side/nonischemic side) |
| Middle ectosylvian gyrus | 0.824 ± 0.196 | 0.115 ± 0.036 | 0.23 ± 0.10 |
| Posterior ectosylvian gyrus | 0.661 ± 0.101 | 0.113 ± 0.027 | 0.21 ± 0.06 |
| Posterior sylvian gyrus | 0.626 ± 0.100 | 0.164 ± 0.036 | 0.31 ± 0.08 |
| Middle suprasylvian gyrus | 0.808 ± 0.157 | 0.185 ± 0.045 | 0.33 ± 0.10 |
| Anterior lateral gyrus | 0.834 ± 0.177 | 0.542 ± 0.120 | 0.68 ± 0.11 |
| Posterior lateral gyrus | 0.819 ± 0.149 | 0.472 ± 0.060 | 0.65 ± 0.11 |
| Central thalamus | 0.790 ± 0.087 | 0.714 ± 0.104 | 0.89 ± 0.05 |
| Lateral geniculate body | 0.964 ± 0.123 | 0.956 ± 0.129 | 1.00 ± 0.05 |
| Central white matter, level of thalamus | 0.193 ± 0.013 | 0.059 ± 0.020 | 0.32 ± 0.11 |

*Arterial Pco₂ = 33.38 ± 0.65 mm Hg.
ischemic hemisphere. The distribution of rCBF changes within the ischemic hemisphere tended to be similar among animals, although the absolute magnitude of rCBF decrements produced by MCA occlusion showed considerable variation among animals. Figure 4 illustrates a representative section from an animal showing profound ischemia within the right MCA territory.

CORRELATION OF PN FLUORESCENCE CHANGE WITH rCBF

For each animal, a “cortical ischemia index” (CII) was computed, defined as an average of the ratios (rCBF ischemic side/rCBF nonischemic side) for the middle ectosylvian, posterior ectosylvian, posterior sylvian, and middle suprasylvian gyri. Linear regression analysis of CII versus peak PN fluorescence (PPNF) produced the equation:

$$\text{PPNF} = -54.8 \times \text{CII} + 47.2$$

with $$r = -0.681$$ (P < 0.05). A similar relationship was obtained for CII versus final PN fluorescence values ($$r = -0.663$$, P < 0.05).

EFFECT OF AMBIENT OXYGENATION UPON CORTICAL PN FLUORESCENCE

To test the hypothesis that the decrease in cortical PN fluorescence observed following MCA occlusion might be accounted for by the gradual shift of the PN redox state toward oxidation due to the effect of ambient oxygen upon the respiratory chain,16 separate experiments were carried out in three cats. In these animals, the exposed cortex and fluorometer dipping cone assembly were isolated from the external environment by means of a flexible plastic cylinder which was flushed continually with 100% nitrogen gas during the control period and following MCA occlusion. Despite the presence of surface nitrogen, the initial rise in cortical PN fluorescence was followed by a decline whose slope was no different from that observed in the earlier studies (range -0.071% to -0.155% per second).

Discussion

The pyridine nucleotide coenzyme NADH stands at the negative end of the chain of mitochondrial respiratory components along which electron transport occurs, resulting in the reduction of molecular oxygen and the generation of high-energy phosphate in the form of adenosine triphosphate (ATP). Previous studies have shown NADH to be the component of the respiratory chain whose redox state correlates most closely with the ability of mitochondria to carry out energy-linked functions.17,18 In metabolically active tissue, in which the levels of endogenous NADH-generating substrate and phosphate acceptor (adenosine diphosphate, ADP) are high, mitochondria are physiologically active (“State 3” of Chance and Williams19) and ATP is generated via oxidative phosphorylation. Under these conditions, approximately 50% or more of pyridine nucleotide may exist in the oxidized form. However, ADP depletion leads to a nearly complete reduction of NAD+ to NADH (mitochondrial State 4).20 The transition from the normoxic to the anoxic state (State 5) may similarly be associated with the complete reduction of pyridine nucleotide.20

When excited by 366-nm light, brain and other tissues have been shown to undergo fluorescence emission in a broad band with emission maxima at 472 nm; during the transition from aerobicosis to anoxia the emission intensity abruptly increases but a shift in the emission spectrum does not occur.21 This 440 to 480-nm emission band corresponds to that of mitochondrial-bound NADH. Cytoplasmic pyridine nucleotide may undergo reduction as well, but this is known to happen at a much slower time course.21

Hypoxia and ischemia thus may bring about an increase in tissue PN fluorescence. However, both the excitation light and the emitted PN fluorescence may be attenuated or scattered by non-fluorescing tissue pigments such as hemoglobin. Changes in vascular volume produced by arterial occlusion and subsequent tissue hypoxia lead to fluctuations in the amount of extravascular hemoglobin in the field of observation and thus would be expected to produce variable and unpredictable degrees of interference with the fluorescence signal. Furthermore, spectral shifts occurring during the hemoglobin-oxyhemoglobin transition result in considerably different tissue reflection spectra during normoxia and anoxia.22 Thus, the reliable quantitation of fluorescence data presupposes careful correction for these potential sources of artifact. In the present study, the latter problem was overcome by measuring fluorescence at 445 nm, which is an isosbestic point for reduced and oxyhemoglobin and in addition lies near the fluorescence emission peak of NADH. The problem of varying vascular volume was approached by means of a technique in which transient perturbations of intravascular hemoglobin concentration are produced by brief saline flushes delivered via the lingual artery.23 From the maximal deflections produced, one can calculate a ratio of (fluorescence change/reflection change), which can be employed to obtain a fluorescence value which has been corrected for variations in hemoglobin (see Methods). Harbig et al.,24 using a closed-skull preparation, found this ratio to be approximately one in all animals under defined conditions, whereas Jobsis et al.,25 in an open preparation, found the ratio to vary with different preparations and among different fields of the same preparation. In our study, employing an open-skull preparation, this ratio proved to be...
constant within any given optical field but varied from 1.1 to 2.5 (average 1.6) in the various fields studied in our animal series. In the squirrel monkey, Sundt and Anderson⁴ failed to observe significant alterations in cortical reflected light during systemic hemodilution or following MCA occlusion, but they employed an optical system which differed in several respects from that of the present study.

Artifacts produced by respiratory activity or arterial pulse were not observed in this study despite the use of an exposed brain preparation. In addition, fluorescence and reflected signals were free of significant drift during control periods of 20 to 30 minutes. The various sources of artifact in these preparations have been considered in detail by Harbig and co-workers.⁹

The brisk rise observed in the corrected pyridine nucleotide fluorescence signal following MCA occlusion in this study denotes an abrupt reduction of pyridine nucleotide occurring within seconds of the onset of ischemia. The rapidity of this intracerebral NADH increase is incompatible with substrate depletion but rather suggests a marked slowing of mitochondrial respiration. The maximal increase in NADH fluorescence observed in most animals of this study was somewhat less than that produced by nitrogen anaesthesia,⁸ suggesting that intracellular hypoxia was not total. Chance et al.¹⁸ have estimated that a 50% reduction of NAD⁺ from its normoxic level corresponds to an intracellular oxygen tension of approximately 0.07 mm Hg, depending to a degree upon the metabolic activity of the tissue. Normal oxygen utilization may be possible until the intracellular oxygen tension declines below 0.5 to 1 mm Hg.⁷

We have shown that the decline in NADH fluorescence following its initial rise cannot be explained on the basis of ambient oxygen near the cortical surface, nor on the basis of instrumentation drift. Photodecomposition of fluorescent substances may occur during exposure to exciting light of high intensity, but this phenomenon appears to have a more protracted time course.²⁰ Furthermore, inasmuch as significant amounts of NADH are present in the normoxic cortex, one would have expected to observe a decline in the cortical fluorescence signal during the control period as well if photodecomposition had been present. Finally, in studies of nitrogen anaesthesia using an identical apparatus, photodecomposition was not observed. Thus it appears unlikely that photodecomposition played a role in the decline in fluorescence signal during the first minutes following ischemia.

The consistent decline in NADH fluorescence observed in the normotensive animals and its lesser prominence in the hypotensive animals of this series suggest that this may have been caused by increased tissue oxygenation related to the entry of circulation into the ischemic zone via collateral channels. Both the peak PN fluorescence values and the final PN fluorescence values observed several minutes later correlated significantly with rCBF measurements made two to 15 minutes following the onset of ischemia, but it is possible that the rCBF decrement produced by the initial vascular occlusion was greater than that observed several minutes later. Evidence that a small increase in CBF may suffice to cause reoxidation of NADH is provided by the study of compression ischemia reported by Harbig and Reivich.⁵¹

When intracranial pressure was elevated to reduce cerebral perfusion pressure (CPP) to zero for up to six minutes, an increase in NADH fluorescence of up to 40% of full scale occurred; a subsequent increase in CPP of as little as 5 mm Hg was sufficient to cause progressive partial reoxidation of NADH. In a recent study, LaManna and co-workers examined cortical redox state following subclavian and/or innominate artery occlusion in the cat.³ Occlusion of either vessel alone was associated with a rapid NADH fluorescence increase followed by a decline to baseline within two minutes, whereas occlusion of both vessels produced a sustained NADH fluorescence plateau similar to that produced by terminal anaesthesia. Thus, in the present model of partial cerebral ischemia with the availability of collateral channels, small restitutions of flow following ischemia may enable NADH to be reoxidized. In the squirrel monkey, Sundt and Anderson failed to observe a decline in NADH fluorescence during MCA occlusion; however, they noted higher NADH fluorescence plateaux during MCA occlusion in hypotensive hypovolemic animals than in those which were normotensive and normovolemic.⁵ In that study, removal of the MCA clip following one hour's occlusion resulted in a prompt decline in NADH fluorescence to normal levels.⁴

An alternative explanation for the decline in NADH fluorescence during ischemia in our study is that there is reoxidation of NADH as a consequence of a depression of local cerebral metabolism triggered by the ischemic insult. Consistent with this possibility are the observations of Sundt and Waltz,²² of which focal ischemia may be associated with the presence of hyperoxygenation of the local venous blood occurring without an associated increase in cortical blood flow, implying that there exists a failure of local oxygen utilization. Bruce et al.²⁴ have reported, in studies of compression ischemia, that as CBF is reduced from 50% of normal to 40%, there is a sudden increase in the cerebral metabolic rate for glucose, associated with a decrease in the cerebral arteriovenous difference for oxygen. Thus, at certain critically reduced levels of cerebral perfusion, oxygen utilization may be actively inhibited, concomitant with an acceleration of anaerobic glycolysis. In the present study, local CBF values fell to 33% or less of the control hemisphere values in the four most ischemic gyri (see table 2), and it is possible that inhibition of oxygen utilization may have occurred.

The rCBF decrements produced by MCA occlusion in this study are, on the average, somewhat greater than those reported in the squirrel monkey by Blair and Waltz²⁵ and tend to fall within the range of rCBF values obtained by the krypton method in the cat by Waltz under conditions of halothane anesthesia.²⁶

In summary, the results of this study indicate that acute MCA occlusion in the cat is associated with an abrupt, though short-lived, increase in cortical NADH levels, implying a disturbance of cortical oxidative metabolism. The mechanisms by which cortical NADH is apparently reoxidized despite the persistence of ischemia require further investigation. Two possible mechanisms are suggested: (1) a re-entry of circulation into the ischemic zone via collateral channels, and (2) an active inhibition of oxygen utilization in the ischemic region.
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