Local Cerebral Blood Flow Following Transient Cerebral Ischemia

I. Onset of Impaired Reperfusion within the First Hour Following Global Ischemia

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SUMMARY Using the hydrogen clearance technique, local cerebral blood flow (LCBF) in 22 dogs was estimated at 6 parietal sites prior to and following 5 min of total global ischemia. Ischemia was immediately followed by an initial reactive hyperemia during which the electrocorticogram (ECoG) usually began to recover, and within the first 30 min, most of the LCBF's decreased to subnormal values. This onset of hypoperfusion was accompanied by a concomitant decrease in ECoG activity. Two animals that maintained normal local perfusion after the initial hyperemia recovered ECoG activity quickly. These results suggest that the subsequent poor reperfusion was caused by an increased microvascular resistance rather than by blood aggregates, increased blood viscosity, or a variety of other mechanisms which have been proposed. Increased vascular tonus was, at least, partly responsible for the increased vascular resistance. This report supports the hypothesis that impaired reperfusion (which occurs some time after an initial hyperemia) may be responsible for ultimate neuronal death, rather than the period of global ischemic hypoxia per se.

SEVERAL REPORTS have indicated that the vulnerability of the central nervous system to brief periods of ischemic hypoxia may be due to impaired recirculation, rather than to immediate cell death. Hossmann, Lechtape-Gruter, and Hossmann demonstrated the return of neuronal functions (EEG, pyramidal response, evoked potentials) in cats after 30 or 60 minutes of complete cerebral ischemia. Hossmann and Kleihues concluded that normothermic nerve cells can withstand 60 min of complete ischemia and that revival of nerve cells is hindered (presumably) by deficits in recirculation. Additional support to this hypothesis has been given by Yatsu, Lee, and Liao and others who have shown that cerebral energy metabolism is not always irreversibly damaged and is not primarily vulnerable to ischemia.

The cause of impaired cerebral microcirculation following ischemia has been attributed to many factors. Ames and co-workers concluded that the "no-reflow phenomenon" was due to increased blood viscosity and endothelial and perivascular glial cell swelling. Fischer and Ames noted that perfusion deficits appeared in a scattered pattern and did not appear to be caused by platelet microemboli or pial arterial spasm. Chiang et al. implicated swollen endothelial "blebs" which they claimed obstructed the capillary lumen. Little, Kerr and Sundt related impaired microcirculation to the compression of capillaries by perivascular glial swelling, but also noted that severe neuronal injury preceded the microvascular obstruction. Conversely, Cuypers and Matakas concluded that no-reflow was produced by blood aggregates which obstructed larger vessels rather than capillaries. Wade et al. proposed that the no-reflow state is due to an increase in potassium concentration in brain extracellular fluid which causes a pronounced contraction of vascular smooth muscle. Klatzo concluded that arterial spasm was responsible for the no-reflow phenomenon. Hekmatpanah demonstrated capillary microthrombi and red cell aggregates during circulatory standstill. Microcirculatory blockage has also been attributed to consumption coagulopathy and to an "ischemic tissue-blood interface" reaction that reduces blood flow by an unspecified mechanism.

Some investigations have shown that cerebral ischemia may be initially followed by hyperemia, but with a subsequent hypoperfusion within one hour. During the initial post-ischemic hyperemia, the cerebral mean requirement of oxygen (CMRO₂) may be temporarily reduced, but the CMRO₂ may subsequently increase beyond control values. Perfusion deficits, accompanied by an elevated CMRO₂, result in a prolonged cerebral hypoxia that may contribute to post-ischemic cerebral pathogenesis. The etiology of perfusion deficits has still not been resolved which emphasizes the need to investigate post-ischemic cerebral circulation so that methods of restoring adequate blood flow may be devised.

The purpose of this investigation was to closely follow the changes in local cerebral blood flow after total ischemia and to determine whether there was any evidence to support (or reject) the hypothesis that cerebral recovery may be hindered by poor reperfusion rather than by immediate death of hypoxic nerve cells.

Methods

Anesthesia was induced in adult, healthy mongrel dogs, 15 to 25 kg, with intravenous thiopentone sodium (Intraval, May & Baker) and maintained with
intravenous pentobarbide sodium (Sagatal, May & Baker) on demand. Following endotracheal intubation and insertion of femoral arterial and venous catheters for pressure monitoring and blood sampling, artificial ventilation was maintained with air and oxygen (40% O₂), 20 breaths per minute, at a tidal volume which kept the arterial PCO₂ at about the normal canine level of 38 mm Hg. This PCO₂ produced an end-expired CO₂ (FECO₂) typically between 4.5% and 5% as measured by a Godart Capnograph. A Radiometer BMS Mk2 blood microsystem was used for serial measurement of arterial pH and blood gases. Body temperature was maintained at 38°C and was continuously monitored using a rectal thermistor. The ventilation system was computer controlled as described by Lampard, Coles, and Brown.31

A Cardiovascular Instrument cardiac output computer, which employs the thermodilution technique, was used for cardiac output estimates. A thermistor was firmly fixed in the pulmonary artery with a purse string suture; bleeding from the artery was slight and transient.

Local Cerebral Blood Flow Measurement

The hydrogen clearance technique was used for estimating local cerebral blood flow. Hydrogen clearance curves were essentially monoexponential with a small second order effect. Only the first order exponential segment by dividing the half-time (time in seconds taken for the function to decay to half its initial value, \( A_0 \)) by 0.693; multiplication of \( k \) by 60 yields the local cerebral blood flow in units of ml blood/minute/100 gm tissue.

Platinum wire of 0.3 mm was silver soldered to 1 mm Belling-Lea connectors and insulated with Epoxy-lite 6001 thermosetting epoxy. Insulation (0.5 mm) was removed from the electrode tip. This insulation technique yields an electrode which is impermeable to physiological fluids or saline for at least 24 hours. Absolute insulation of the electrode is a prerequisite in obtaining inter-electrode independence and smooth, noiseless graphs. If the electrode resistance dropped below 20 megohms, considerable "cross-talk" occurred among electrodes, which resulted in unstable baselines, and it became difficult to properly bias the electrodes to +300 millivolts. Adequate electrode insulation against ultimate leakage is a commonly encountered problem, especially in chronic preparations, as more fully discussed by Donaldson.24

Following reflection of the frontal and temporal muscles along the external sagittal crest, the parietal bone was perforated lateral to the sagittal sinus with a No. 4 dental burr, care being exercised to avoid abrasion or laceration of the dura. In the event of bleeding from the bone the hole was stoppered with bone wax; otherwise, bleeding was slight or unnoticeable. Because of extreme differences among mongrel skulls, it was not possible to stereotaxically implant the electrodes. However, electrodes were standardly placed in parietal lateral, ectolateral, and middle suprasylvian areas at depths ranging from 1 to 8 mm. A rigid micromanipulator was used to prevent electrode movement and minimize tissue trauma while the electrodes were fixed to the skull with Surgical Simplex bone cement. Consistent blood flow measurements from acutely implanted platinum electrodes depends on the immobilization of the electrode after insertion and on the absence of subdural bleeding. An electrode depth of at least 1 mm was necessary to avoid inaccurate flow estimates resulting from the rapid diffusion of hydrogen from the surface of the cortex.28 Local cerebral blood flow estimates were measured from 5 or (usually) 6 electrode sites in each dog.

Tissue damage during electrode insertion may preclude reliable washout curves until healing has occurred,24 27 but a series of experiments in this laboratory showed LCBF estimates to be constant under controlled conditions.26 Stainless steel Sherman bone screws were located parieto-occipitally as the reference electrodes for the platinum electrodes. The epidural electrocorticogram (ECoG) was measured from bilateral Sherman bone screws inserted into frontal bone. Bone screw depth was carefully matched to skull thickness to avoid compression of the cortex with the screw tip. Epidural intracranial pressure (ICP) was measured using a stainless steel adapter inserted into parietal bone. Care was taken to ensure that there was no bleeding from the bone that would clot the lumen of the ICP adapter.

Mean arterial pressure (MAP), systolic pressure, diastolic pressure, pulse rate, FECO₂, I.C.P., rectal temperature, and the mean rectified voltage (MRV) of the ECoG were recorded continuously on a Brush 8 channel recorder.

Technique for Producing Total Cerebral Ischemia

Following a left thoracotomy and removal of the fourth rib, the brachiocephalic and left subclavian arteries were exposed and cotton thread was passed under each artery near its origin. A length of Silastic tubing (3 mm o.d.) was passed twice around the descending aorta to form a loop. This loop allowed complete constriction of the aorta when the ends of the Silastic tubing were drawn. Dissection around the heart and ascending arteries was cautiously performed to avoid any trauma to the vagosympathetic trunk, cardiovagal branches and other nerves in the area.

Because of the collateral circulation to the dog brain arising from the descending aorta, complete cerebral ischemia cannot be achieved by clamping only the brachiocephalic and left subclavian arteries. However, if the descending aorta is also occluded, it is necessary to provide a pressure vent (or "shunt") for the left ventricle to prevent blood congestion in the heart and lungs. To provide this shunt, a catheter was passed from the femoral artery into the aortic arch. During the ischemia, this catheter allowed diversion of
arterial blood to a one liter Viaflex bag (Travenol Labs).

To produce the total cerebral ischemia, the brachiocephalic and left subclavian arteries were clamped at their origin. Assuming 86 ml blood per kg body weight, heparin was injected intravenously at a dose of one unit per ml blood. Immediately after the heparin injection, the intra-aortic catheter was connected to a one-liter plastic blood collection bag (Travenol Viaflex) and the descending aorta was constricted around the intra-aortic catheter by drawing the ends of the Silastic loop. Blood returned from the blood collection reservoir via the femoral vein. It is important that the catheters have the widest possible lumen so that blood can flow rapidly and freely into and out of the blood bag.

The ECoG became flat (isoelectric) typically within 30 seconds and this flattening served as the starting point of the 5 minute period of ischemia. At the end of 5 minutes of isoelectric ECoG, the constriction around the descending aorta was removed, the clamps were removed from the ascending arteries, and the intra-aortic catheter was withdrawn. Arterial Pco₂ quickly returned to pre-ischemia levels (36–40 mm Hg), but arterial pH was predictably low. Arterial pH was corrected by intravenous infusion of 4.2% sodium bicarbonate at 1 ml/minute until pHₐ was within a normal range (7.36 to 7.44); usually, this required about 60 to 80 ml of 4.2% bicarbonate. Bicarbonate was not infused until the local blood flows were demonstrated to be reduced below control values. Simultaneous LCBF estimates were recorded from 6 electrode sites in each dog, except for 3 animals which had 5 electrode sites. This resulted in a total of 117 electrode sites for the 20 dogs used in these experiments.

Results

The mean LCBF was 43.0 ml/min/100 gm tissue, with a standard error of ±4.8 ml/min/100 gm and a range of 19 to 198 ml/min/100 gm. The wide range and relatively large standard error emphasize the heterogeneity of flow around cortical and subcortical electrode sites. For ease in comparative analysis each post-ischemic LCBF is expressed as a percentage of its pre-ischemic control value of 100%. Figure 1 shows the local cerebral blood flow from 6 electrode sites for one representative dog. Each symbol represents an electrode site. Pac₀₂ was normal within 5 minutes after the ischemia and the pH, was corrected to 7.4 after one hour. Note that most flows remain subnormal during subsequent hours.

Initially decreased below control when cranial circulation was restored. After the ischemic episode, it took at least 5 minutes to reposition the animal, rebias the electrodes and resume estimates of LCBF's. After the initial hyperemia, blood flows appeared to decrease relatively gradually (fig. 2), but occasionally a precipitous drop in blood flow was noted. This was exemplified by a sudden decrease in the wash-out of hydrogen and the introduction of a significant second order component in the decay curve (fig. 3). This acute decrease in flow is a difficult event to capture using a gas clearance method. In one animal, there was a simultaneous acute decrease in flow at 3 of 6 electrode sites. This was accompanied by a marked decrease in the ECoG mean rectified voltage.

Intracranial pressure (ICP) was never elevated during the period of flow decrease. During the ischemia, ICP always decreased, indicating the partial emptying of blood from the cerebral venules and a reduction in cerebral blood volume. Following restoration of the circulation, ICP usually increased sharply (not more than 40 mm Hg) and then recovered to pre-ischemic levels of about 3 mm Hg within 10 minutes (fig. 4). In subsequent hours, the ICP never showed a tendency to increase.

Figure 1. Changes in local CBF at 6 electrode sites for one representative dog. Each symbol represents an electrode site. Pac₀₂ was normal within 5 minutes after the ischemia and the pH, was corrected to 7.4 after one hour. Note that most flows remain subnormal during subsequent hours.
After restoration of circulation, end-expired CO₂ was elevated, but returned to normal within 5 to 10 minutes. The post-ischemic arterial pH was between 7.25 and 7.3, and was not corrected with sodium bicarbonate during the first hour post-ischemia. It was believed best to avoid the complication of introducing another variable to the many physiological alterations that were happening during and immediately after the ischemia. Bicarbonate may have varying effects depending on the rate of intravenous infusion and the rate of change of the cerebrospinal fluid pH. Also, it was important to initially observe the behavior of the post-ischemic brain blood flow without interference from other therapies or drugs. The only resuscitative action consisted of adequate ventilation and restoration of blood pressure and cardiac output. When pHₘ was corrected (typically 1 to 1.5 hours after ischemia), sodium bicarbonate (4.2%) was infused at a rate not exceeding 0.05 ml/min/kg. The correction of pHₘ did not cause any significant increase or decrease in LCBF.

Cardiac output (CO) was not measured in all animals but measurements in 3 animals showed an immediate post-ischemic increase in CO that returned to nearly normal within the first hour. In most animals, the increase in cardiac output was accompanied by a transient hypertension (150 to 190 mm Hg systolic BP) that decreased to no less than 120 mm Hg systolic.
LOCAL CBF AND THE ECoG FOLLOWING ISCHEMIA

21 JULY 78
P \(_{CO_2}\) 38mmHg

start pHa

CORRECTION

LOCAL CBF % OF CONTROL

100

50

0

ISCHEMIA

0 1 2 3 4 5 6 7 HOURS

LOCAL CBF

300

250

200

150

100

50

0

ECoG MRV (µV)

40

20

0

-20

-40

0 1 2 3 4 5 6 7 HOURS

ICP

40

20

0

-20

-40

0 1 2 3 4 5 6 7 HOURS

FIGURE 4. Slight recovery of the ECoG during hyperemia, and the subsequent decrease in ECoG following the decrease in LCBFs.

BP. The difference between systolic and diastolic pressures was at least 30 mm Hg. Heart rate was normal or slightly increased. These cardiovascular measurements demonstrated that reduced LCBFs were not due to cardiovascular impairment. This also emphasizes that the technique for producing the ischemia preserves heart function. It is important to have a healthy heart after the ischemia so that changes in LCBF can be confidently ascribed to the cerebral vasculature rather than to a failing heart and a milieu of supportive drugs.

The electrocorticogram (ECoG) is a sensitive indicator of the decrease of LCBFs following the initial hyperemia. During the initial post-ischemic hyperemia, the ECoG mean rectified voltage (MRV) began to gradually recover, but then there was a subsequent decrease concomitant with the reduction in LCBFs (fig. 4). This effect was noted in 14 of the 20 animals. In the remaining 6 dogs, the ECoG MRV remained nearly isoelectric during the hyperemia. Even though the local flows remained depressed, most of the animals gradually recovered control levels of ECoG MRV within 8 hours following ischemia. Recovery of electrocorticographic activity was defined as the return of ECoG MRV to approximately 100% of the control (pre-ischemic) levels. In 2 animals, the ECoG MRV recovered quickly to control levels and the LCBFs did not decrease below control after the initial hyperemia. These 2 dogs were apparently not as vulnerable to ischemia as the other 20 dogs and, therefore, have not been included in figure 2.

During ischemia, the pupils were fully dilated. When circulation was re-established, the pupils recovered normal diameter (about 2 mm) within 10 minutes. Mild and transient convulsions and tremors were observed during and after the ischemia; these events typically subsided within the subsequent hour. Because of the ischemic insult, the animals did not require any further anesthetic. The animals had typically been anesthetized for 6 to 8 hours prior to ischemia.

Discussion

Five minutes of ischemia was chosen as this period is reported to be the threshold for irreversible brain damage in animals and man. Other studies have shown that animals may survive 12 to 15 minutes of ischemia and have an apparent clinical recovery and normal EEG, but these periods are long in comparison to the shorter periods compatible with permanent damage. Although several studies have shown that energy metabolism returns quickly after ischemia, resumption of cerebral metabolism does not imply recovery of cerebral function. In animals it is difficult to assess clinical recovery in terms of subtle changes in fine motor skills, personality, and intellect.

Definite histological evidence of brain damage may be accompanied by a normal scalp EEG and apparent clinical recovery. In the present experiments, we were interested in the initial changes in cerebral blood flow that may contribute to neuronal death. These results show that 5 minutes of total cerebral ischemia in dogs caused an initial reactive hyperemia that was succeeded by a decrease in local cerebral blood flows to subnormal levels. Thirty minutes after ischemia, most of the flows had fallen to subnormal levels (figs. 1, 2). Not all the electrode sites recorded an initial hyperemia. Within the first 10 minutes, 9 of 92 electrode sites recorded an initial hyperemia. Within the first 10 minutes, 9 of 92 electrode sites recorded subnormal blood flows (fig. 2). It is not possible to determine whether these electrode sites were initially hyperemic and then decreased before resumption of recording, or whether flows were depressed upon restoration of arterial flow.

The ECoG was a sensitive monitor of the hyperemia and the subsequent decrease in local CBFS. The post-ischemic rise in the ECoG activity (during hyperemia) was followed by a diminution of ECoG activity that was concomitant with the LCBF reduction to subnormal levels (fig. 4). This decrease in LCBFs was seen in 20 of 22 dogs. The remaining 2 animals displayed an initial hyperemia that was followed by LCBFs returning to approximately normal values; the ECoG mean...
rectified voltage (MRV) recovered quickly to control levels within 2 hours in these animals.

The decrease in LCBF could be a normal response to reduced oxygen demand by the brain; a reduced CMRO₂ would be expected to result in lower LCBFs. Hossmann et al.⁴⁶ correlated CMRO₂ with post-ischemic recovery in cats. Post-ischemic CMRO₂ was always reduced within the first hour after ischemia, but then increased to normal levels. If the O₂ uptake remained low, the animals had no electro-physiological recovery but if O₂ uptake returned to normal, animals showed good recovery. Yatsu et al.⁴ concluded that the energy metabolism was not primarily vulnerable to ischemia and that the machinery for energy synthesis remained intact following 5 minutes of ischemia. In fact, rather than metabolism being depressed after 5 minutes of ischemia, mitochondrial ATP synthesis was greater than control. Schutz et al.⁴ also reported brain mitochondrial function to be intact after ischemia. Nemoto⁴⁴ reported that after 16 minutes of ischemia in cats, the CMRO₂ was not different from control CMRO₂ within the first 30 minutes after ischemia; over the subsequent 2 hours, CMRO₂ increased by 2-fold.

Catecholamine release during ischemia has been shown to increase CMRO₂, a condition that may lead to a secondary hypoxia if oxygen availability is not proportionately increased.¹⁸

Post-ischemic brain hypermetabolism may incite neuron damage.¹⁸ After global ischemia in dogs, Snyder et al.⁷ noted a reduced CMRO₂ and CBF coincident with an abnormally low cerebral venous oxygen content, which indicated that a hypoxic state existed. They negate “the idea that post-ischemic reduction in CBF is simply a matching of CBF to reduced cerebral metabolic demands (reduced CMRO₂)”. Lang et al.⁴¹ also concluded that post-ischemic reduced CBF is not a normal response to reduced CMRO₂; decreased oxygen consumption was the result of metabolic derangement and reduced oxygen availability.

The present experiments did not measure CMRO₂, but we believe that it is unlikely that diminished CBF after ischemia is a normal consequence of a non-injurious reduced CMRO₂. Because of the possibility of normal or elevated O₂ demand, reduced CBF may represent a post-ischemic hypoxia that may initiate nerve cell death. The reduced local blood flows (within 30 minutes post-ischemia) seen in these experiments are most likely causing an oxygen debt that is being reflected by the concomitant decrease in ECoG activity (fig. 4).

These results indicate that a general “no-reflow” phenomenon was not present following the ischemic insult, but that gross impairment of local reperfusion occurred some time after the resumption of arterial flow. This is in contrast to other investigations which have reported that vessels develop blockage during (or immediately subsequent to) the ischemia.⁶,⁷,⁹,¹¹,⁴² Hence it appears that the impairment in reperfusion occurs well after the end of ischemia. The initial rise in ECoG activity was followed by a decrease that coincided with the decrease in local CBF. It is tempting to speculate that the ECoG would have recovered quickly if the post-ischemic LCBFs could have been maintained at normal or supranormal levels.

The hyperemia may be explained by vasodilatation due to tissue acidosis from lactic acid and carbon dioxide, or by a slight increase in extracellular potassium.⁴³ Some of the increases in local blood flow were remarkable. For example, one electrode site went from a control flow of 35 ml/min/100 gm to a postischemic flow of 230 ml/min/100 gm. Figure 2 shows that 27 flows were initially greater than 400% of control.

It is unlikely that transient brain swelling associated with hyperemia was responsible for a subsequent artificial decrease of LCBF around each electrode site. In previous experiments from this laboratory,⁴² hypercapnea was never followed by low LCBF when the animals were returned to normocapnea; similarly, when animals were hyperventilated,⁴³ a return to normocapnea was never associated with LCBF changes from previous control values.

Other investigators have reported a reactive hyperemia following either total or focal ischemia. Cuypers and Matakas⁴¹ found that sustained hyperemia (either spontaneous or sympathomimetically induced) was beneficial in preventing post-ischemic no-reflow and intracranial hypertension. Osburne and Halsey⁴⁴ reported that post-ischemic hyperemia in gerbils was associated with ultimate clinical and EEG recovery; regional blood flows demonstrated a reactive hyperemia that later declined to subnormal levels. Hossmann et al.¹ reported that post-ischemic hyperemia was a prerequisite for the recovery of brain electrical activity; their results also demonstrated a transient phase of hyperemia that was followed by generally subnormal cerebral blood flow.⁴⁵ Safar et al.⁴⁶ showed that therapeutic measures aimed at improving the cerebral circulation resulted in eventual clinical recovery following 12 minutes of cardiac arrest in dogs. Our results suggest, that initial hyperemia may be beneficial in restoring the ECoG, and only when the hyperemic phase ended, did the ECoG demonstrate an abrupt decrease in activity (fig. 4).

Conversely, Mchedlishvili et al.⁴⁶ concluded that post-ischemic hyperemia is a contributory factor in the development of brain edema. Heiss et al.⁴⁷ also concluded that reactive hyperemia in focal (middle cerebral artery occlusion) ischemia appeared to potentiate cerebral edema. Other investigations have also implicated hyperemia as a harmful consequence of ischemia⁴⁸-⁶⁰ but some of these involved prolonged focal ischemia and/or induced arterial hypertension; therefore, comparisons with transient ischemia and reactive hyperemia (without arterial hypertension) may not be valid and should be interpreted cautiously. When comparing these results against those from other laboratories, it is important to recognize the differences in experimental design and duration of ischemia. While the conclusions drawn by other in-
vestigators are usually convincing, the methodologies are often so different as to make comparisons difficult. This is an important consideration and is further emphasized by Molinari and Laurent.

The results of these experiments do not support some hypotheses presented by other investigators concerning the etiology of “no-reflow.” Obstruction of capillaries by swollen astroglia, blood aggregates and thrombi, microthrombi, swollen erythrocytes and increased blood viscosity have been implicated as major antecedents of “no-reflow.” Wade et al. reported that high concentration of extracellular potassium and consequent vascular constriction may account for “no-reflow.” However, if any of these effects were significant contributors to the derangement of local CBF, then it would be expected that these would be manifest by initial low flows. It may be possible to mount an argument that may explain how one of the above hypotheses may have a delayed effect after a period of hyperemia. In all our experiments, ischemia was immediately followed by hyperemia. Even at those sites which displayed depressed initial flows, LCBFs were between 52% and 89% of control (fig. 2). This is an “impaired reflow” rather than a “no-reflow” and implies vascular narrowing rather than occlusion. Only at later times (30 to 60 minutes) did the LCBFs become so seriously decreased as to constitute in some instances a nearly “zero” flow.

It is uncertain whether the hyperemia per se was responsible for the subsequent decrease in LCBFs. While some reports have concluded that excess reperfusion may contribute to brain edema, none of the animals in the present experiments demonstrated raised ICP after the hyperemic phase. Local edema (e.g., perivascular glial swelling) may have developed, but if this were a significant effect, then the ICP would be expected to become elevated because most of the LCBFs were subnormal, and widespread local edema (affecting nearly all the local flows) would be expected to show itself by raised ICP. Hyperemia may have caused extravasation, rupture of weak endothelia, or sloughing of intraluminal “blebs.” Chiang et al. discovered diffuse intraluminal “blebs” which were more frequent 30 minutes after ischemia. However, Fischer et al. have reinvestigated the “bleb” hypothesis and have concluded that “blebs” may have been artifacts caused by an improper histological perfusion-fixation technique. Also, Little et al. found only minor capillary changes even after hours of ischemia and concluded that these changes did not appear to be producing significant obstruction.

As discussed in Part II, the local vasculature was still highly reactive to increased arterial PCO2 after the ischemia. Of 70 electrode sites, 14 sites did not show an increase in blood flow during hypercarbia; the remaining 56 sites indicated a significant vasodilatation during hypercarbia. These increases in LCBF indicate that the post-ischemic vasculature was not generally paralytic and was not blocked by various cellular aggregates or fragments. The most likely explanation for the reduced blood flows is an increase in cerebral vascular resistance, i.e., a reduction in the caliber of the microvessels. It is not certain whether the resistance is increased by delayed perivascular glial swelling or by a sudden increased vessel tonus. The precipitous reduction in flow at some electrode sites (fig. 3) suggests that increased tonus must be a contributing factor. This sudden flow decrease would be more likely due to smooth muscle contraction rather than to a sudden swelling of many endothelial or perivascular glial cells.

An important consideration in these results is the barbiturate anesthesia, which has been shown to have protective effects in cerebral hypoxia and on ICP. Anesthesia was kept at a relatively light level by giving small doses of pentobarbitone only when the eyelid reflex reappeared. Even though pentobarbitone may reduce the vulnerability of brain cells to hypoxia, 4 to 5 minutes of complete global ischemia is sufficient to cause motor and behavioral disabilities or death. Five minutes of total ischemia and isoelectric ECoG was enough to seriously derange the local CBF's in the present experiments.

It is highly unlikely that any heparin would have been in the cerebral vasculature during ischemia. If thrombi form during ischemia, heparin may inhibit thrombogenesis. Heparin was added after the brachiocephalic and left subclavian arteries were clamped and immediately prior to bypass from the aorta to the external reservoir. After the ischemia, heparinized blood may be beneficial by preventing secondary clotting in areas of low flow or by dissolving thrombi, but others have shown that heparin did not appear to improve post-ischemic recirculation.

These results show that relatively short periods of global ischemia (but sufficient to incur permanent damage) are followed by generally increased LCBFs. This initial hyperemia may be accompanied by incipient ECoG activity, but when the LCBFs begin to decrease to subnormal levels, ECoG activity becomes markedly depressed. Two animals that maintained normal LCBFs after the initial hyperemia recovered ECoG activity quickly. Results suggest that subsequent hypoperfusion was due to microvascular narrowing and that increased vascular tonus was at least partly responsible for decrease vessel caliber. This report supports the hypothesis that the brain may not suffer severe neuronal death during ischemia, but that recovery may be hindered by microcirculatory deficits.

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References


Local cerebral blood flow following transient cerebral ischemia. I. Onset of impaired reperfusion within the first hour following global ischemia.

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