Regional Brain Po2 After Global Ischemia in Monkeys: Evidence for Regional Differences in Critical Perfusion Pressures

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SUMMARY We measured brain tissue Po2 in the frontal and occipital cortices, mid-brain and basal ganglia in monkeys for up to 5 hours after 16 min global brain ischemia to gain some insight into those factors responsible for the selective vulnerability of the brain to ischemia-anoxia. Brain tissue Po2 measurements were made with gold microelectrodes with tip diameters of 5 to 10 nm. Reoxygenation of the different brain regions occurred at different "apparent" cerebral perfusion pressures and times postischemia. Areas of low susceptibility to ischemic brain damage, such as the frontal cortex, were not consistently reoxygenated at lower perfusion pressures or earlier postischemia than were areas of high susceptibility such as the occipital cortex, basal ganglia and midbrain. These findings support earlier observations that perfusion defects and brain histologic changes are multifocal in nature after global brain ischemia. We suggest that the selective vulnerability of the brain to ischemia is attributable to the development of regional edema and a local increase in tissue pressure during ischemia thereby decreasing cerebral perfusion pressure and leading to local perfusion defects after restoration of circulation. Also, that the selective vulnerability of the brain is attributable to variable degrees of neuronal-glial edema and regional shifts in brain water during ischemia leading to the development of local perfusion defects and the expansion of lesions from areas of high to low vulnerability.

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THE SELECTIVE vulnerability of the brain to ischemia-anoxia was recognized as early as 1858 by Brown-Sequard.1 To explain this phenomenon, O. Vogt2 and C. Vogt3 hypothesized a greater sensitivity of neurons to "toxic factors" (i.e., pathoclisis) while Spielmeyer4 suggested a major role of "vascular factors" such as arterial compression and vascular obstruction. Scholz5 proposed that the selective vulnerability of the brain was due to a combination of both toxic and vascular factors.

Present-day proponents of these earlier hypotheses are Ames and associates6,7 (vascular factors) and Brierley and associates5 (pathoclisis). Chiang et al.8 showed that vascular obstruction occurred as a result of endothelial "bleb" formation, capillary "pinching" due to swollen astrocytic foot processes, and red blood cell and platelet aggregation. Brierley argued that the "no-reflow phenomenon" does not explain the selective vulnerability of the brain because so anatomically diffuse a process as vascular obstruction does not account for the frequently observed lumenal destruction of cortical layers or viable neurons adjacent to dead neurons. There is little doubt that neuronal death after ischemia can occur without the no-reflow phenomenon as shown by Levy and Plum9 but this does not preclude some role for perfusion defects in the pathogenesis of ischemic brain damage. Indeed, we10 and Hossmann et al.11 have clearly demonstrated delayed development of brain hypoperfusion within 1 hour after global brain ischemia (GBI).

Our aim in this study was to determine whether the magnitude and time course of brain reoxygenation postischemia differed in areas of high and low susceptibility to ischemic damage. Briefly, our results show that the different brain regions are reoxygenated at different "apparent" cerebral perfusion pressures (CPP) but that the highly susceptible areas (i.e., occipital cortex, midbrain and basal ganglia) were not predictably reoxygenated later or at higher CPPs than less susceptible areas (i.e., frontal cortex).

Methods

Anesthesia and Surgical Procedures

Five young, healthy, female rhesus monkeys (Macaca mulatto) weighing from 4 to 5 kg were rendered analgesic with 70 percent N2O/30 percent O2 and immobilized with pancuronium (Pavulon) at 0.1 mg/kg body weight i.m. The monkeys were intubated with cuffed endotracheal tubes lubricated with 4 percent lidocaine (Xylocaine) and mechanically ventilated on 0.5 to 1.0 percent halothane/70 percent N2O/30 percent O2 plus CO2 to maintain continuously monitored end-tidal CO2 at approximately 5 percent. Bipolar ECG electrodes were attached and peripheral intravenous lines were inserted for continuous infusion of 5 percent dextrose/0.45 percent NaCl at 3.5 ml/kg/hr. Transurethral bladder catheters were inserted for continuous monitoring of urine output. Catheters inserted into the femoral arteries and veins were used for arterial blood pressure monitoring,
blood sampling and intravenous drug infusion. The cuffed endotracheal tubes were then changed to rigid teflon endotracheal tubes to enable mechanical respiration during ischemia induced by a high pressure neck tourniquet and arterial hypotension. The monkeys' heads were fixed in a stereotoxic apparatus and biparietal stainless steel screw EEG electrodes were fixed on the calvarium over the parietal cortices. Silastic catheters were inserted subdurally over the parietal cortex for continuous monitoring of intracranial pressure (ICP).

Insertion of the Po2 microelectrodes was accomplished via craniotomies over the appropriate areas. Po2 microelectrodes were stereotaxically inserted into the following brain regions: frontal cortex (FC), in the area of the mid-frontal gyrus; occipital cortex (OC), at the level of the calcarine fissure 5 mm from the midline; midbrain (MB), in the region of the oculomotor nucleus; and the basal ganglia (BG) in the region of the caudate nucleus. These areas of high and low susceptibility to ischemic anoxic damage were previously determined in monkeys subjected to 16 min GBI with neurologic deficit scoring until sacrifice at 7 days postischemia. The microelectrodes were advanced into the different brain regions with an attempt to obtain Po2 values between 0 to 20 torr. After insertion of the microelectrodes, all craniotomies were sealed with dental methyl methacrylate cement.

A 30 min stabilization period followed insertion of the microelectrodes when all instrumentation was recalibrated and normal values of the following variables were verified: mean systemic arterial pressure (SAP) 80–125 torr; rectal temperature, 37–39°C; and ICP, less than 20 torr. An arterial blood sample was obtained to confirm normal arterial blood pressure (SAP) 80–125 torr; rectal temperature, 37–39°C; and ICP, less than 20 torr. An arterial blood sample was obtained to confirm normal arterial blood values (i.e., PaO2 > 100 torr; PaCO2, 35–40 torr; and pH 7.35–7.45).

Global brain ischemia was induced for 16 min by a combination of trimethaphan camsylate (Arfonad) hypotension to a mean SAP of about 50 torr and a high pressure (1500 torr) neck tourniquet with controlled hypotension throughout ischemia as previously described. After 16 min GBI, the monkeys were ventilated on 100 percent O2 and SAP was gradually restored to between 100 to 120 torr by titrated intravenous norepinephrine (Levophed) infusion. End-tidal CO2 was maintained at about 5 percent and arterial blood oxygen saturation was obtained at 5, 30, 60, 120, 180, 240, and 360 min postischemia. Although attempts were made to keep PaO2 and PacO2 within the limits previously described, correction of pH by sodium bicarbonate infusion was avoided as much as possible because of its profound effects on brain Po2 (see Results). At the end of the study, the brains were perfused and fixed with 4 percent paraformaldehyde. Two hours later, the brains were removed from the calvarium for verification of microelectrode tip positions by serial sections and microscopic examination of hematoxylin-eosin stained tissue.

The Po2 microelectrodes were constructed according to the methods described by Erdmann et al. Glass-covered gold wires 10 to 25 μm diameter were beveled and polished to tip diameter of about 5 μm and coated with Rhoplex (Rhom-Hass). Microelectrodes for insertion into the midbrain and basal ganglia were specially constructed in glass capillary pipettes with shank lengths ranging from 3–5 cm. The microelectrodes were calibrated in 100 percent N2, 5 percent O2/N2 and room air in 0.9 percent NaCl at 37°C. The Po2 amplifiers used were as previously described by Kunke et al. All recordings were made with the animals entirely enclosed in a Faraday cage.

Results

The importance of maintaining precise control of physiologic variables and the effect of experimental manipulations on brain tissue Po2 was demonstrated preischemia in 2 of the monkeys. Rapid intravenous infusion of sodium bicarbonate (fig. 1) decreased SAP to about 50 torr and increased end-tidal CO2 to 7 percent. In one minute, Po2 in the frontal cortex and basal ganglia fell to 0.5 and 20 torr, respectively. An abrupt increase in ICP (fig. 2) from 8 to 26 torr by infusion of 0.9 percent NaCl into the subarachnoid space caused a precipitous decrease in both frontal cortex and basal ganglia Po2.

In the first study (fig. 3), preischemic Po2 in the frontal cortex and basal ganglia was 44 and 5 torr, respectively. Trimethaphan hypotension to a MAP of about 50 torr decreased Po2 in both regions. The magnitude of the decrease appeared to be in proportion to initial resting values. Po2 decreased rapidly to 0 torr with inflation of the neck tourniquet but ischemia was terminated after 9 minutes when ventricular fibrillation necessitated resuscitation. Upon restoration of circulation, frontal cortex Po2 rapidly rose to 80 torr in the first 4 minutes postischemia while basal ganglia Po2 increased slowly to 15 torr between 5 and 6 minutes postischemia. Thereafter, Po2 in both regions gradually declined until 32 minutes postischemia. Rapid intravenous infusion of dextran 40 (Rheomacrodex) increased Po2 only transiently.

In the second study (fig. 4), Po2 measurements were made in the frontal cortex, basal ganglia and midbrain with preischemic values of 6, 13 and 2 torr, respectively, at a CPP of 120 torr and ICP of less than 10 torr. Trimethaphan reduction of SAP decreased Po2 in all areas in proportion to resting values as observed in the previous study (see fig. 3). After 16 min ischemia, reoxygenation occurred first in the midbrain at a CPP of 20 to 30 torr at 2 min postischemia. Frontal cortex and basal ganglia Po2 did not increase until 5 min postischemia. After 5 min of reperfusion when CPP reached 60 torr, basal ganglia Po2 rapidly rose to 20 torr whereas frontal cortex Po2 gradually rose to 5 torr at 30 min. Severe brain edema developed and ICP increased to 40 torr. Between 30 and 160 min postischemia, Po2 in all regions fell in spite of a constant CPP and a CPP of 160 torr. Between 160 and 190 minutes, a rapid increase in ICP to 100–120 torr with a fall in CPP to 60 torr decreased Po2 to 0 torr in all
FRONTAL CORTEX PO$_2$ (torr)

BASAL GANGLIA PO$_2$ (torr)

CVP (torr)

SAP (torr)

ETCO$_2$ (%)

ICP (torr)

FIGURE 1. Monkey brain tissue PO$_2$ in the frontal cortex and basal ganglia (area of the caudate nucleus) during intravenous infusion of 7 ml NaHCO$_3$. CVP = central venous pressure, SAP = systemic arterial pressure, ETCO$_2$ = end-tidal CO$_2$. 

0.25% HALO / 50% N$_2$O / 50% O$_2$
regions. Norepinephrine infusion caused a sharp rise in CPP from 10 to 60 torr without affecting Po2. The histologically verified electrode positions were as follows: basal ganglia, medial to the subthalamic nucleus; frontal cortex, gray matter of the cingulate gyrus; and midbrain, in the periaqueductal gray matter.

In study 3 (fig. 5), Po2 was successfully recorded in the frontal cortex, basal ganglia, midbrain and occipital cortex with preischemic values of 5, 8, 0.5 and 3 torr, respectively, at a CPP of about 110 torr. As in the earlier studies, a decrease in CPP to 50 torr preischemia decreased Po2 in all brain regions in proportion to the resting values. Postischemia, CPP was 80 torr and was increased to 120 torr within 2 minutes. As a result, Po2 in all regions rapidly rose and the magnitude of the increase in Po2 was proportional to the preischemic values. Frontal cortex was reoxygenated earliest postischemia and sustained high Po2s were observed in all regions between 3 and 12 min. At 1 hour postischemia, CPP was 80 torr and Po2 in the frontal cortex, midbrain and occipital cortex was less than 5 torr. Cardiac arrest at 240 min caused a rapid fall in Po2 to near 0 torr in the frontal cortex, but was maintained at 10 torr in the basal ganglia. An increase in CPP by norepinephrine infusion increased Po2 in all regions.

In study 4 (fig. 6) preischemic Po2 in frontal cortex, basal ganglia and occipital cortex was 8, 0 and 11 torr, respectively, at a CPP of 120 torr and ICP of 5 torr. After 16 minutes of ischemia, frontal cortex Po2 rose to 1 torr immediately upon tourniquet deflation at a CPP of 25–30 torr. CPP was deliberately and slowly increased from 25 to 140 torr over 20 min in an attempt to magnify the difference in CPP required for reoxygenation of the different brain regions. Although frontal cortex Po2 increased immediately postischemia, a greater rise was not observed until CPP reached 40 torr. A marked increase occurred when CPP reached 60 torr. Po2 in the basal ganglia remained at 0 torr until a CPP of 60–70 torr was attained then rapidly increased to greater than 40 torr with a rise in CPP to 140 torr. Occipital PO2 did not begin to increase until a CPP of 100 torr was attained.

**FIGURE 2.** Monkey brain tissue Po2 in the frontal cortex and basal ganglia (area of the caudate nucleus) during abrupt increase in intracranial pressure (ICP) from 8 to 26 torr by intracisternal injection of 0.9 percent NaCl. CVP = central venous pressure, SAP = systemic arterial pressure, ETCO2 = end-tidal CO2.

**FIGURE 3.** Frontal cortex (FC) and basal ganglia (BG) Po2 after 9 minutes global brain ischemia by high pressure (1500 torr) neck tourniquet and trimethaphan hypotension in the rhesus monkey. Mean systemic arterial pressure illustrated in top panel.
FIGURE 4. Frontal cortex (FC), basal ganglia (BG) and midbrain (MB) PO2 after 16 minutes global brain ischemia by high pressure (1500 torr) neck tourniquet and trimethaphan hypotension in the rhesus monkey. ICP = intracranial pressure, CPP = cerebral perfusion pressure (i.e., mean SAP minus ICP).

FIGURE 5. Frontal cortex (FC), basal ganglia (BG), midbrain (MB) and occipital cortex (OC) PO2 after 16 minutes global brain ischemia. (See legend of figure 4 for details.)
After reaching peak values at a CPP of 140 torr, \( P_{O_2} \) fell in all brain regions despite a sustained high CPP. By 2 hours postischemia, \( P_{O_2} \) in both the frontal and occipital cortex was below preischemic levels. The occipital cortex electrode tip was located between the first and second cortical layers.

In study 5 (fig. 7), \( P_{O_2} \) was measured in the frontal and occipital cortices and midbrain. Again, the differences in reoxygenation times and perfusion pressures were demonstrated in the different brain regions. Midbrain \( P_{O_2} \) increased in 1 min postischemia at a CPP of 60 torr, whereas it remained close to 0 torr in the frontal and occipital cortex until a CPP of 80 torr was attained. The decrease in CPP and \( P_{O_2} \) between 10 and 12 min postischemia was due to cardiac arrest which was immediately corrected by external cardiac massage. CPP was restored to 120 torr. Despite a sustained high CPP between 12 and 360 min postischemia, \( P_{O_2} \) in all brain regions gradually fell below preischemic levels.

**Discussion**

Tissue \( P_{O_2} \) indicates the balance between oxygen supply and consumption within the sensitive volume of tissue estimated to have a radius of 10 to 20 \( \mu \)m for a 5 \( \mu \)m diameter electrode. Po2 alterations occur as a result of changes in \( O_2 \) supply (i.e., blood flow, hemoglobin-\( O_2 \) affinity, diffusion coefficients for \( O_2 \) in blood and brain, etc.) and consumption. When continuously monitored and compared in a normal state to that in an altered or pathological state, \( P_{O_2} \) values yield qualitative information on relative changes in \( O_2 \) availability, especially if evaluated by the construction of \( P_{O_2} \) frequency histograms.

Normal brain tissue \( P_{O_2} \) values ranging from 0 to 100 torr have been reported with values of greatest frequency in the range of 5 to 30 torr. \( P_{O_2} \) values of 0 torr recorded with microelectrodes as we observed in some cases, are not indicative of brain tissue hypoxia unless it has fallen to 0 torr from a higher value. \( P_{O_2} \) associated with mitochondrial hypoxia as evaluated by half-maximal oxidation of NADH and cytochrome c were 0.06 and 0.03 torr, respectively, beyond the accuracy of the \( P_{O_2} \) microelectrodes.

The range of \( P_{O_2} \) values recorded in brain has been attributed to \( P_{O_2} \) gradients along capillaries and to regional variations in capillary density. Both are plausible explanations since changes in \( P_{O_2} \) of 20 to 30 torr over distances of 50 to 100 \( \mu \)m are likely due to capillary or vascular gradients whereas regional capillary density effects may be revealed by frequency histograms. However, while Cross and Silver reported higher \( P_{O_2} \) in gray matter and lower \( P_{O_2} \) in...
white matter, Nix and Halsey\cite{Nix1980} reported exactly the opposite in rat spinal cord. Namely, the \( P_o_2 \) was lower in gray matter and higher in white matter presumably due to the higher metabolic rate of gray matter. Our attempt to seek \( P_o_2 \) values of 0–20 torr was based on the reasoning that gray matter areas would have higher metabolic rates and lower \( P_o_2 \)s. Also, that areas with similar \( P_o_2 \)s would be alike in terms of \( O_2 \) supply and utilization and may thus be comparable in terms of absolute \( P_o_2 \) changes between different brain regions. The validity of our reasoning, however, is unverified.

The magnitude and rate of change in regional \( P_o_2 \) at the start of ischemia and upon reperfusion appeared to be proportional to the initial value. Therefore, the time required for \( P_o_2 \) to fall to 0 torr during ischemia was similar in all regions in a given study regardless of the initial value. Postischemia, the peak \( P_o_2 \) values obtained were in most cases highest for areas with high initial values. This phenomenon has been noted by other investigators\cite{Becker1980, Hockberger1980, Zipes1980, Heistad1980, Halsey1980} and is probably related to the capillary density of the region. Areas with high capillary density also have a greater reactivity to \( CO_2 \).\cite{Niswander1980}

Our results show that different brain regions are reoxygenated at different CPPs after global brain ischemia. We attribute the difference in reoxygenation to regional variations in critical perfusion pressure (i.e., that perfusion pressure required to reperfuse a given area of the brain after an ischemic insult). The extrapolation from reoxygenation to tissue perfusion assumes that the differences in reoxygenation are not due to variable rates of oxygen consumption. We believe that this assumption is at least valid within the first hour postischemia since during this time brain oxygen consumption is depressed\cite{Kloner1980, Siesjö1980} and is not likely to be a major determinant of regional \( P_o_2 \). Beyond 1 hour postischemia, however, oxygen consumption may be back to normal\cite{Nygren1980, Siesjö1980} or even greater than normal\cite{Siesjö1980} and may significantly influence local \( P_o_2 \). Therefore, we speculate that the differences in reoxygenation early postischemia are due to variable critical perfusion pressures. A number of related observations support this speculation. First, functional recovery of the brain after GBI is a function of the degree of reperfusion established.\cite{Bickford1980} Second, brain histological changes are multifocal in nature.\cite{Bickford1980} Third, the severity of postischemic hypoperfusion is reduced by increased perfusion pressure postischemia.\cite{Hockberger1980} It is important to note that the occurrence and importance of the no-reflow phenomenon has been questioned since the initial observations by Ames and associates.\cite{Ames1980} Indeed, these authors have retracted their findings upon subsequent evaluation.\cite{Ames1980} However, there is still substantial evidence demonstrating multifocal cerebral hypoperfusion postischemia and its pathogenesis remains to be determined.

Differences in apparent regional critical perfusion

\[ \text{FIGURE 7. Frontal cortex (FC), basal ganglia (BG) and occipital cortex (OC), } \]
pressure may result from reduced regional CPP due to: a) variable degrees of regional edema causing an increase in local tissue pressure; b) variable degrees of vasomotor tone or vasospasm induced by local metabolites or neurotransmitters (i.e., catecholamines). The precise mechanism of regional variation in critical perfusion pressure after GBI remains to be determined, but the importance of providing CPPs in the hypertensive range (i.e., 150–200 torr) to establish reperfusion of all areas immediately postischemia has been emphasized by Hossmann et al.12 Leniger-Follert and Hossmann12 showed that high CPPs early postischemia were correlated with early and rapid reoxygenation of all areas measured in the cat cortex.

The lack of consistently delayed reoxygenation postischemia in areas of high susceptibility is not surprising since brain histologic evaluations reveal that ischemic brain damage is "patchy" and multifocal in nature.6,9,12 That is to say, an area of low susceptibility is evident only because the frequency of infarction is lower and not because it does not occur at all. The construction of Po2 frequency histograms for the different brain regions would probably distinguish areas of low and high susceptibility by showing a net shift of highly susceptible areas towards lower Po2s than less susceptible areas.

In summary, we have shown that different regions of the brain are reoxygenated at different cerebral perfusion pressures which may explain the selective vulnerability of the brain to ischemia-anoxia. These findings stress the importance of the no-reflow phenomenon in the pathogenesis of ischemic brain damage and of maintaining an "adequately" high CPP early postischemia. However, it must not be construed that arterial hypertension of any magnitude or in any form should improve recovery after GBI. Hossmann12 reports that there appears to be an optimal CPP for recovery while Bleyaert et al.16 showed that repetitive, intermittent arterial hypertension increased neurologic deficit in monkeys.

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Pathophysiological Mechanisms of Brain Edema Development: Role of Tissue Factors

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SUMMARY In experiments carried out on adult rabbit “chest-head” preparations the volume changes of the exposed brain (BrV) were determined in repeated tests during a controlled increase of the systemic venous pressure (SVP) of about 13 mm Hg. The changes of both SVP and BrV were usually parallel at the onset of the experiments, but when the brains became preedematous hysteresis appeared in the plots of their relationships. The hysteresis increased gradually (sometimes with periods of partial decrease) thus indicating a delay in the draining of blood from the brain’s venous system and in the removal of excess extracellular fluid from the cerebral tissue. Evidence for water filtration through the capillary walls during increase of the SVP, and, thus, of brain intravascular pressure, was obtained by detecting the dynamics of [Na+] and [K+] in the extracellular fluid of the cerebral cortex by ion-selective electrodes. This process appeared reversible in normal brains while in the preedematous ones the excessive water filtration resulted in brain edema. The preedematous state of the brain is believed to be caused by changes of the mechanical properties of brain tissue and/or by changes in osmolarity.

THE PATHOPHYSIOLOGICAL mechanisms of brain edema development have been reviewed by I. Klatzo who described 2 main causes of cerebral edema — vasogenic and cytotoxic. According to Klatzo, vasogenic edema is caused by an increase in capillary permeability, while cytotoxic edema develops without such changes. An increase in vascular permeability during brain edema has attracted the attention of a number of investigators whose experimental results showed that different tracers, which normally did not penetrate the cerebral vascular walls when administered into the blood stream, were detected in the cerebral tissue with different kinds of brain tissue damage and subsequent edema development.

These data do not establish that increased vascular permeability is the crucial mechanism in the development of brain edema. The role of circulatory factors in the development of brain edema is certainly very important, since the edema is defined as excess accumulation of water in brain tissue and a main source of water is the blood circulating in the cerebral vasculature. Also, the level of the systemic arterial pressure plays an important role in the rate of edema development. However, a considerably more important role in the development of brain edema has been shown recently to be played by the systemic venous pressure. In spite of the significance of circulatory factors, these factors appear to play a secondary role in the development of brain edema since the retention of water within the cerebral tissue seems to be dependent primarily upon tissue changes. Unfortunately, there is still very little knowledge of the nature of the cerebral tissue changes responsible for development of edema. Attention has been focused on 2 kinds of changes. In the early 1960s it was assumed that changes in the mechanical properties of cerebral tissue were important for development of brain edema, but no experimental evidence to prove this assumption has been obtained so far. Second, an increase in osmolarity of

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Abstract, p 684
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