Brain Blood Flow and Metabolism
After Global Ischemia and Post-insult
Thiopental Therapy in Monkeys

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SUMMARY We measured total and regional cerebral blood flow (CBF, rCBF) and cerebral metabolic rate (CMR) of oxygen (O$_2$), glucose (G), and lactate (L) levels for 4 h after 16 min global brain ischemia in rhesus monkeys with and without post-insult thiopental therapy. Eleven monkeys weighing 4–5 kg anesthetized with 1 percent halothane, 66 percent nitrous oxide and 33 percent oxygen, were subjected to 16 min global brain ischemia by a combination of trimethaphan hypotension (to a mean arterial pressure of 50 torr) and a high pressure (1500 torr) neck tourniquet. Post-ischemia, 7 monkeys were untreated (controls) and 4 received thiopental 90 mg/kg infused intravenously over 60 min, beginning at 5 min post-ischemia. Total CBF and rCBF were measured by continuous monitoring of cerebral venous (torcula) and parietal-occipital (external scintillation) 133Xe activity, respectively, after intra-innominate artery injection of 500 μCi 133Xe in saline. In control monkeys, hyperemia in CBF, but not in total CBF was observed at 6–7 min post-ischemia, whereas both total CBF and rCBF increased in thiopental treated monkeys. The hyperemia in thiopental treated monkeys coincided with an increase in CMR without a proportional increase in CMRO$_2$ or lactate levels. Indeed, CMRO$_2$ was depressed in the first 30 min post-ischemia. At 30 min post-ischemia, CMRO$_2$ rose to twofold greater than pre-ischemia in control monkeys, but only to pre-ischemic levels in thiopental treated monkeys. The data suggest that thiopental therapy improves distribution of brain blood flow and brain glucose uptake early post-ischemia and depresses CMRO$_2$ later post-ischemia.

Methods and Materials

Eleven prequarantined and fasted female rhesus monkeys weighing 4–5 kg (Primate Imports, Inc.) were anesthetized with halothane, 4 percent pure oxygen, injected intramuscularly with 0.4 mg atropine and 0.08 mg/kg pancuronium bromide and their tracheas intubated with cuffed endotracheal tubes. Their lungs were mechanically ventilated by a fixed volume time-cycled piston respirator (Harvard Apparatus, Inc.) on 1 percent halothane, 66 percent nitrous oxide and 0.08 percent oxygen plus CO$_2$. Endtidal CO$_2$ was continuously monitored (Beckman LB-1 infrared analyzer) and maintained between 5 and 6 percent by manipulation of inspired CO$_2$.

Sodium chloride 0.9 percent, was infused at 3–5 ml/kg/h via peripheral venous catheters. EKG leads were attached and transurethral bladder catheters and rectal thermistors were used for continuous monitoring of urine output and rectal temperature. Femoral artery and vein catheters were inserted for arterial blood sampling, drug infusions and monitoring of mean arterial pressure (MAP). Catheters inserted in the right brachial artery (catheter tip in the innominate artery) were used for 133Xe in saline injection for CBF and rCBF measurements (fig. 1). The external carotid arteries were bilaterally ligated to minimize extracranial contamination of CBF measurements.

Supradural electroencephalogram (EEG) screw electrodes were inserted over the parietal-occipital cortex and subdural, supracortical catheters inserted...
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sampled at a rate of about 7 ml/min, passed through a glass monitored for at least 10 min after isotope injection. "Flush" volume 0.2 ml was used. External carotid arteries bilaterally ligated to reduce extracranial contamination of rCBF measurements. Brain $^{133}$Xe measured over the parietal-occipital cortex by the scintillation probe anchored into position. Simultaneously, cerebral venous blood from the torcular was continuously sampled at a rate of about 7 ml/min, passed through a glass coil on the face of a shielded scintillation probe and returned to the monkey via the femoral vein. Brain $^{133}$Xe activity was monitored for at least 10 min after isotope injection.

FIGURE 1. Systems for measurement of total CBF (top right) and rCBF (top left) in the monkey. Right brachial artery catheter for $^{133}$Xe-saline (500 μCi) 0.2 ml with the catheter tip in the innominate artery for bilateral carotid delivery of the isotope. "Flush" volume 0.2 ml was used. External carotid arteries bilaterally ligated to reduce extracranial contamination of rCBF measurements. Brain $^{133}$Xe measured over the parietal-occipital cortex by the scintillation probe anchored into position. Simultaneously, cerebral venous blood from the torcular was continuously sampled at a rate of about 7 ml/min, passed through a glass coil on the face of a shielded scintillation probe and returned to the monkey via the femoral vein. Brain $^{133}$Xe activity was monitored for at least 10 min after isotope injection.

over the parietal cortex for intracranial pressure (ICP) monitoring. Angiocaths (18 ga), inserted into the torcular were connected to an extracorporeal circulation system (fig. 1) for continuous sampling of cerebral venous blood. A focused collimated scintillation probe was fixed over the parietal-occipital cortex for rCBF measurements. A 30 min stabilization period was allowed before measurements were begun.

Pre-ischemic measurements of CBF and rCBF with arterial and cerebral venous blood sampling for oxygen content, glucose, lactate, pH, PO$_2$, PCO$_2$ and hematocrit were made during 1 percent halothane, 66 percent nitrous oxide, and 33 percent oxygen anesthesia. Arterial and cerebral venous blood samples were simultaneously withdrawn immediately before isotope injection, changed to 1 sec for 1 min after peak activity, then changed to 5 sec for the remaining 9 min or longer of monitoring. The clearance curves were recorded on a dual pen strip chart recorder (Linear Instruments, Inc.) for at least 10 min after isotope injection.

Calculations of CBF and rCBF from the clearance curves were done by the height/area method$^{18,19}$ using a Graf-Pen-3 (Scientific Research Corp.) in line with model 600-14 Wang computer using the formula shown below.

$$ CBF \text{ or } rCBF = \frac{\text{peak height}}{\text{peak area}} = \frac{\text{ml/100 g/min}}{\text{corrected for hematocrit according to the equation}}. $$

where:

$$ \chi = \frac{1.04}{C + 0.787(1-C)} \left( \frac{0.744}{0.3} \right) \text{ hematocrit} \left( \frac{1}{34} \right) $$

μCi $^{133}$Xe in 0.2 ml saline was injected intraarterially and the tourniquet rapidly (< 1 sec) inflated to 1500 torr. During ischemia, MAP was controlled at 50 torr. Complete arrest of brain $^{133}$Xe clearance during ischemia verified complete ischemia in each study. Titrated intravenous norepinephrine (0.016 mg/ml) begun 2–3 min before the end of ischemia was used to raise MAP to 100 torr before deflation of the tourniquet and continued post-ischemia to maintain MAP between 80 to 120 torr. CBF and rCBF were measured at 6 (i.e., 1 min after the start of thiopental infusion), 15, 30 min and every 30 min thereafter for up to 240 min post-ischemia. Brain metabolic rates of oxygen, and glucose and lactate excretion were measured at similar intervals, but not at 90, 150 and 210 min post-ischemia. Post-ischemia, the monkeys were ventilated on 100 percent oxygen and the following pharmacologic interventions were used: a) Furosemide, one mg/kg for oliguria; b) lidocaine in 10 mg boluses for cardiac dysrhythmias; c) isoproterenol, for A-V conduction blocks; d) trimethaphan, (one mg/ml) for MAP greater than 125 torr; e) norepinephrine for MAP less than 80 torr; and f) sodium bicarbonate, for base excess greater than minus 5 mEq/l.

Both total and regional CBF were simultaneously measured. Regional CBF was estimated by continuous monitoring of cerebral venous $^{133}$Xe activity by a scintillation probe with a specially designed lead shield for the glass coil. The output of both probes were fed into a dual channel spectrometer-ratemeter (Nuclear Chicago) with the windows set for the 81 KeV peak of $^{133}$Xe. The ratemeter time constant was set at 0.05 sec before isotope injection, changed to 1 sec for 1 min after peak activity, then changed to 5 sec for the remaining 9 min or longer of monitoring. The clearance curves were recorded on a dual pen strip chart recorder (Linear Instruments, Inc.) for at least 10 min after isotope injection.

where: $\chi = \frac{1.04}{C + 0.787(1-C)} \left( \frac{0.744}{0.3} \right) \text{ hematocrit} \left( \frac{1}{34} \right)$
1.04 = Xe brain/blood partition coefficient for 60 percent gray matter and 40 percent white matter at a hemoglobin concentration of 17 g/100 ml or a hematocrit of 57 percent.

Average blood values for rhesus monkeys are: hemoglobin, 12.6 grams/100 ml; hematocrit; 42 percent; and mean corpuscular hemoglobin concentration, 30.18.

Arterial and cerebral venous pH, PCO$_2$ and PO$_2$ were measured with a Corning model 175 trielectrode blood gas unit. Blood glucose and lactate were analyzed by enzymatic methods$^{19,20}$ and oxygen content by the Lexicon Oxygen Content Meter.

Calculated physiologic variables were as follows: Cerebral perfusion pressure (CPP) = mean arterial pressure (MAP) minus intracranial pressure (ICP); cerebrovascular resistance (CVR) = CPP/CBF; and cerebral metabolic rate (CMR) for oxygen (O$_2$), and glucose (G) = A-V difference × CBF; and oxygen utilization coefficient (O$_2$UC) = CMRO$_2$/CBF × arterial O$_2$ content.

In some cases, statistical analyses were done using log or square root transformations to stabilize the variance for analysis of variance. Significance among groups of means were tested with the Student-Newman-Keuls test at the 0.05 level.$^{22}$

Results

Mean arterial pressure in control and thiopental treated monkeys was maintained at about 100 torr throughout the study (except during ischemia) with a range of mean values between 87 ± 7 (SEM) and 113 ± 6 torr. Mean ICP at 6 min post-ischemia in thiopental monkeys (27 ± 7 torr) was higher ($p < 0.05$) than in controls (17 ± 2 torr), but was otherwise similar in both groups. In the first 15 min post-ischemia, arterial pH in controls was 7.28 ± 0.03 and lower ($p < 0.05$) than in thiopental treated monkeys (7.41 ± 0.02). PaO$_2$ was about 100 torr pre-ischemia and greater than 400 torr post-ischemia while mean PaCO$_2$ ranged between 32 ± 1 and 45 ± 4 torr in both groups. Hematocrit ranged between 33 ± 3 and 40 ± 2 percent and rectal temperature was maintained within a range of 37.9 ± 0.1 to 38.2 ± 0.3° C.

Pre-ischemic CBF and rCBF (fig. 2) in both groups was about 70 to 80 ml/100 g · min$^{-1}$. Total CBF at 6 min post-ischemia (i.e., 60 secs after the start of thiopental infusion) in thiopental monkeys increased

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Cerebrovascular variables before and after 16 min global brain ischemia in seven untreated control monkeys (•••••••) and 4 monkeys treated with thiopental 90 mg/kg infused intravenously over 60 min beginning at 5 min post-ischemia (○○○○○). Global ischemia was induced by trimethaphan hypotension (mean arterial pressure = 50 torr) and a high pressure (1500 torr) neck tourniquet. Total cerebral blood flow (CBF) and regional cerebral blood flow (rCBF) were measured simultaneously after intra-arterial injection of $^{133}$Xe in saline (500 μCi) by continuous monitoring of cerebral $^{133}$Xe activity, and external scintillation detection of parietal-occipital activity by a focused collimated scintillation probe. Post-ischemia, mean arterial pressure was restored by titrated intravenous norepinephrine infusion.$^{*}$ $^{*}$ = p < 0.05 compared to pre-ischemic value.
to 133 ml/100 g • min⁻¹ compared to 70 ml/100 g • min⁻¹ in controls. By 30 min total CBF in the thiopental group fell to 47 ml/100 g • min⁻¹ and was maintained at about that level for up to 240 min. Total CBF hyperemia observed in thiopental monkeys at 6 min post-ischemia was not seen in control monkeys. Cerebrovascular resistance in thiopental monkeys fell at 6 min post-ischemia (p < 0.05) while not significantly altered in control monkeys.

Pre-ischemia, rCBF was about 80 ml/100 g • min⁻¹ and immediately after recirculation fell to about 60 ml/100 g • min⁻¹ in both groups then increased at 6 min post-ischemia to 113 and 135 ml/100 g • min⁻¹ in control and thiopental groups, respectively. Thereafter, rCBF in both groups fell to 40 ml/100 g • min⁻¹ (approximately 50 percent of the preischemic value) and fluctuated between 30 and 40 ml/100 g • min⁻¹. Pre-ischemic and post-ischemic cerebral perfusion pressures were similar at about 90 torr in both groups.

In the first 60 min post-ischemia, CMRO₂ increased by about 200 percent in control monkeys whereas in the therapy group, it fell by 40 percent (p < 0.02) then returned to control values by 60 min (fig. 3). After 60 min, CMRO₂ remained at 160 percent of pre-ischemia in controls compared to 80 and 90 percent in thiopental monkeys. Mean CMRG in therapy monkeys at 6 min post-ischemia, rose sharply by 950 percent, fell to about 150 percent, then fluctuated between 75 and 225 percent. In contrast, mean CMRG in the untreated control group was only 175 percent of control at 6 min post-ischemia then ranged between 50 and 150 percent. Because of data variability, however, significant differences between the 2 groups were not observed.

Changes in lactate a-v differences (fig. 3) were not observed between the 2 groups and the data were combined for statistical analyses. At 6 min post-ischemia, lactate a-v differences increased (p < 0.05) to 320 percent of pre-ischemia, fell sharply to pre-ischemic levels by 60 min post-ischemia and thereafter ranged between about 50 and 100 percent. Changes in O₂UC were similar in both groups, but appeared to be lower in the thiopental group after 120 min post-ischemia.

In the thiopental monkeys, arterial glucose increased from 5.65 μmoles/ml at 6 min post-ischemia to a peak value of 8.55 μmoles/ml at 60 min (fig. 4). In controls it gradually increased from 4.78 μmoles/ml at 6 min to 7.69 μmoles at 240 min. At 30 and 60 min post-ischemia, arterial glucose was higher in the thiopental compared to the control group. In general, cerebral venous glucose followed the pattern observed for arterial glucose. The norepinephrine required to maintain MAP from 5 to 120 min post-ischemia in thiopental monkeys was between 0.34 and 0.63 mg/h and higher (p < 0.05) than for controls which required

![Figure 3](http://stroke.ahajournals.org/)

**Figure 3.** Cerebral metabolic variables in rhesus monkeys before and after 16 min global brain ischemia. Global brain ischemia induced by trimethaphan hypotension (MAP = 50 torr) and high pressure (1500 torr) neck tourniquet. Post-ischemia, 7 monkeys were untreated (*) and 4 were treated with thiopental (90 mg/kg) infused intravenously over one h beginning at 5 min postischemia (○ ○ ○ ○ ○). Mean arterial pressure restored by titrated intravenous norepinephrine infusion. Cerebral metabolic rate (CMR) for oxygen (O₂) glucose (G) and lactate (L) = total CBF × A-V difference. Total CBF measured by continuous monitoring of the cerebral %Xe activity after intra-arterial bolus injection. * = p < 0.05 compared to controls at the corresponding time period. + = p < 0.05 compared to preischemia.
FIGURE 4. Development of arterial hyperglycemia and correlation with norepinephrine infusion in 7 control monkeys (• - •) and 4 monkeys treated with thiopental 90 mg/kg (○ — ○) infused intravenously over one h beginning at 4 min post-ischemia. Monkeys infused with thiopental required greater (p < 0.05) amounts in the first 120 min post-ischemia compared to controls. Between 150 and 240 min post-ischemia, similar amounts of norepinephrine were required in both groups.

Discussion

The reactive hyperemia in rCBF in control monkeys followed by a decrease to one-half of normal agrees with earlier findings in dogs and cats using the same method for rCBF measurements. The absence of hyperemia in terms of total CBF in control monkeys also agrees with our findings in cats subjected to 16 min global brain ischemia using the same techniques for total CBF as in this study. If rCBF increases without an increase in total CBF as observed in control monkeys, perfusion to other regions must fall. The increase in both total CBF and rCBF in thiopental treated monkeys indicates that the post-ischemic imbalance of blood flow in controls was prevented or corrected by thiopental and that while cortical flow increased, perfusion of other regions was at least maintained. These differences in thiopental and control monkeys were not attributable to differences in CPP, PaO₂ or PaCO₂.

The heterogeneity of regional brain perfusion after ischemic anoxia has been demonstrated using colloidal carbon revealing areas of low perfusion after global ischemia and C-antipyrine rCBF measurements after focal ischemia in cats. In an earlier study, we obtained indirect evidence of regional differences in reperfusion after 16 min global ischemia in monkeys. After recirculation, local brain tissue PO₂ measurements indicated that reoxygenation occurred at different "apparent" cerebral perfusion pressures; thus, some areas were reperfused more easily than others. The reasons for the variations in regional perfusion after cerebral ischemic anoxia are unclear. However, there are several likely explanations. First, during ischemia, regional edema may develop causing an increase in local tissue pressure thereby reducing local perfusion pressure and blood flow. In support of this concept, we found that during global ischemia, osmolality in different regions increases at different rates and magnitudes and may lead to varying degrees of local brain edema during the insult. Second, if vasospasm is involved, it may occur to varying degrees in different regions. An increase in extracellular potassium to levels in excess of 30-40 mEq/l induces vasospasm and has been implicated as a factor in failure of reperfusion after global ischemia. Our results suggest that the efficacy of thiopental may occur through the reduction of brain edema and redistribution of blood flow in different brain regions.

CMRO₂ changes in thiopental treated monkeys appeared to parallel the changes observed in control monkeys, but were generally lower. It is important to note that pre-ischemia the monkeys are anesthetized with halothane which depresses CMRO₂ by about 30 percent. Halothane was discontinued within 5 to 10 min during ischemia and the monkeys were unanesthetized post-ischemia. Therefore, the degree of reduction in CMRO₂ in the first 30 min post-ischemia is probably greater than our data show, whereas the magnitude of the increase in CMRO₂ in controls may be overestimated by 30 percent. These findings corroborate the observations of Nordstrom, et al who reported CMRO₂ reduced within the first 30 min post-ischemia in rats subjected to 15 min global ischemia. The lower CMRO₂ in thiopental treated monkeys compared to controls suggests that the efficacy of thiopental may be related to local improvement of brain oxygenation secondary to a reduction in CMRO₂. However, oxygen utilization coefficient was unaltered in thiopental treated monkeys compared to controls except at 120 min post-ischemia.

The marked increase in CMRG in the first 15 min post-ischemia in thiopental treated monkeys was not accompanied by a proportional increase in CMRO₂ as one would expect if the glucose was being oxidized. Indeed, CMRO₂ was subnormal indicating either an
increase in non-oxidative metabolism of glucose or greater glucose re-saturation of the thiopental treated brain. These data support the findings of Hakim, et al. who showed that barbiturates increase the activity of the hexose monophosphate shunt and glucose utilization for synthetic rather than energy-producing (i.e., mitochondrial oxidation) reactions. The marked increase in glucose uptake in thiopental monkeys was also not attributable to an increase in glycolytic activity since changes in a-v lactate differences in both groups appeared to follow identical patterns. Barbiturate therapy had no effect on a-v lactate differences which were well below normal by 2 and 3 h post-ischemia in control and thiopental groups.

Our findings of a rapid early peak in arterial blood glucose at 1 hour post-ischemia in thiopental monkeys compared to the gradual rise in control monkeys with a peak at 4 hours post-ischemia, are consistent with the findings of Oyama, et al. that barbiturate anesthesia with surgical stress results in decreased insulin secretion, increased growth hormone secretion and hyperglycemia. The higher infusion rate of norepinephrine in thiopental treated monkeys may also account for the post-ischemic increase in serum glucose levels. The rapid increase in arterial glucose in the thiopental monkeys may be partly responsible for its efficacy in preventing edema. Dimattio and associates observed that a 1 percent increase in serum osmolality secondary to glucose infusion resulted in a 12 percent decrease in CSF production in rats. The degree of hyperglycemia observed in our thiopental treated monkeys could cause a 4 mOsm/l increase in serum osmolality if one assumes a linear relationship, this could account for a 30 to 40 percent reduction in CSF formation. This is also supported by our earlier studies showing that pentobarbital anesthesia reduced the rate of rise in brain osmolality during ischemia.

In summary, thiopental appears to ameliorate ischemic brain damage by preventing maldistribution of regional blood flow in the early post-ischemic recirculation phase, and by improving glucose delivery and utilization via non-oxidative pathways. Although the reduction in CMRO2 by thiopental indirectly suggests that thiopental may improve brain oxygenation secondary to the reduction in CMRO2, O2UC was similar in both groups.

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References

Body Fluid Oxygen Tension and Prognosis in Patients With Ruptured Aneurysm

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SUMMARY Body fluid gas pressure and electrolytes of patients with ruptured aneurysm were continuously analyzed. Intracranial pressure (ICP) was regulated at a level of 120–100 mm H2O by cerebral ventricular drainage. There was no significant change in the pH, Pco2, HCO3, Na+, K+, Ca++ in the cerebrospinal fluid (CSF) of patients with slight or moderate disturbance of consciousness (lethargic-drowsy state). The PcarO2 of the patients with marked disturbances of consciousness (semicoma-coma) was significantly low. PcarO2 of the patients with cerebral vasospasm was significantly lower than for those without vasospasms. PcarO2/PaO2 was 0.27 ± 0.01 in the patients with vasospasm and 0.50 ± 0.01 in those with no vasospasms. PcarO2 tended to decrease in patients with markedly bloody CSF. When the bloody CSF was cleared by ventricular drainage, PcarO2 increased. PcarO2 did not return to a normal value in the patients with marked disturbances of consciousness despite sufficient arterial oxygen tension. This suggests that PcarO2 and PcarO2/PaO2 should provide a convenient index for the prognosis of patients with ruptured aneurysm.

Methods

Eleven patients with ruptured aneurysm were examined and the clinical findings are shown in table 1. Patients 5 and 7 had multiple aneurysms. All patients were on continuous ventricular drainage and intracranial pressure (ICP) was regulated at a level of 120–100 mm H2O. Cerebral vasospasm was diagnosed by the criteria of Wilkins et al. Clinical symptoms were graded by Hunt’s classification at admission as: 8 patients grade III, 2 grade IV, and 1 grade V. The operation (neck clipping of the aneurysm) was performed in 9 patients. Four patients died as a result of cerebral vasospasm and pulmonary disease.

In both CSF and femoral arterial blood pH, Pco2, HCO3 and Base Excess (BE) were examined simultaneously. Na+, K+, Cl−, Ca++ and total protein in both CSF and peripheral venous blood were also examined at the same time. The study was continued for a maximum of 70 days consisting of 8 patients with hypertensive intracerebral hemorrhage, 6 patients with brain tumor and 7 patients with miscellaneous neurological diseases were examined using the same procedures.
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