Polarographical Measurement of Local Cerebral Blood Flow in the Conscious and Anesthetized Primate

BY JACK M. FEIN, M.D.,* JAMES WILLIS, M.A., JOHN HAMILTON, AND JOHN PARKHURST, B.A.

Abstract:

Polarographical Measurement of Local Cerebral Blood Flow in the Conscious and Anesthetized Primate

This study was undertaken to evaluate the brain hemodynamics of the primate (Macaca mulatta) in the conscious and anesthetized state. A polarographical circuit was utilized for repetitive measurements of local and average total cerebral blood flow in the conscious state, during analgesia/paralysis, and in the anesthetized state. The electrochemical considerations and in vitro testing are described. Blood flow values were highest in sensory and motor cortex (92.5 ± 3.5 ml/100 gm per minute and 86.2 ± 2.6 ml/100 gm per minute), while there were no significant differences found between other regions of association cortex. Mean deep gray matter blood flow values ranged between 57.6 ± 3.8 and 69.2 ± 3.4 ml/100 gm per minute. The mean local blood flow for the centrum semiovale was found to be 19.5 ± 1.2 ml/100 gm per minute and that for pontine tegmentum was 58.1 ± 3.5 ml/100 gm per minute. At any one electrode locus, at steady state levels of arterial blood gases, the reproducibility of blood flow ranged between 11% and 18%. Seventy-five percent nitrous oxide/25% oxygen in combination with a paralytic agent produced a questionably significant drop in caudate nucleus blood flow. The depressant effects of anesthetic doses of sodium pentobarbital on cerebral blood flow, however, were significant at most electrode sites. These data indicate that the measured blood flow rates within small brain volumes are critically affected by barbiturate anesthesia and seriously question the value of published reports in which these agents were utilized.

Additional Key Words

grey matter blood flow values
in vitro testing
hydrogen
barbiturate anesthesia

Introduction

Inert gas clearance techniques for measuring cerebral blood flow were introduced by Kety and co-workers1-2 and further refinements have allowed more precise and regional studies.3,4 To date, there are only a few reports of cerebral blood flow and metabolism in conscious animals. Roth and colleagues8 studied total and regional cerebral blood flow in unanesthetized dogs using strontium-85, chromium-51 and cesium-141 labeled microspheres. They noted that both brain stem and temporal lobes had flows significantly lower than the average for the rest of the brain and a ratio of gray to white matter flow of 4.83 to 1. Moderately severe reactions to the microsphere injections were noted, however, with nystagmus, tonic forepaw contractions, salivation and decerebrate hypertexension. Histological examination of the brains revealed microinfarctions in the medulla, pons, cerebellum and midbrain as well as in the cerebral hemispheres. This degree of microinfarction after injection of the microspheres has also been noted by Kennedy.9 It can be assumed that these latter observations represent significant alterations in cerebral blood flow by the microspheres themselves and pose formidable objections to the acceptance of such data. Landau and colleagues10 utilized radioautography following intravenous injection of CF3I131 to study cerebral blood flow in the unanesthetized cat. These authors obtained values ranging from 138 to 88 ml/100 gm per minute for cerebral cortex, 23 ml/100 gm per minute for cerebral white matter and 87 ml/100 gm per minute for cerebellar nuclei and white matter, respectively.

Betz et al.11,12 employed both a modified Gibbs thermoelectric probe and a heat conductivity element to measure cortical and deep flow in unrestrained cats and dogs. The results were expressed as relative blood flow changes, since the probes could not be calibrated. Powers, Roe and Creel13 in rhesus monkeys and Leatherman and Bean14 in rats both used thermoelectric probes to measure blood flow at selected sites but likewise were unable to express the electric output of the thermocouples in quantitative terms.

Following Aukland, Bower and Berliner’s15 description of the hydrogen dilution technique for the measurement of myocardial and renal cortical blood...
flow, its usefulness in laboratory measurement of cerebral blood flow was also confirmed. Utilizing the hydrogen clearance method, Haining estimated local cerebral blood flow in the unanesthetized rat, and reported an average blood flow value of 79 ml/100 gm per minute in the frontal cortex.

The polarographical technique is particularly suited for measuring cerebral blood flow in the conscious animal. Advantages of the method include the capacity for repetitive and simultaneous determinations from multiple areas in vivo. The purpose of this study was to evaluate the usefulness of the hydrogen dilution technique in measuring the rate of cerebral blood flow in cortical and deep locations within the awake primate brain. The data indicate the local variations of cerebral blood flow rates normally occurring within the waking brain, and their susceptibility to anesthetics which depress cerebral metabolic activity.

Methods

Since hydrogen gas is in diffusion equilibrium between brain and blood, its washout rate is related to the cerebral blood flow rate. Tissue hydrogen concentrations were measured polarographically with platinum electrodes after the technique of Aukland. In polarographical recording, the platinum electrode is held at a constant potential with respect to the reference electrode. This potential is chosen to allow the electrochemical reaction $H_2 \rightarrow 2H^+ + 2e^-$ to occur at a rate proportional to the hydrogen partial pressure. Under these conditions, the current flowing in the external circuit connecting the reference and platinum electrodes will be proportional to the hydrogen partial pressure.

The polarographical circuit was designed to maintain the necessary constant potential between the reference and platinum electrodes, and to detect and amplify the current generated by the hydrogen half cell reaction at the platinum electrode. Figure 1 is a functional block diagram of this device. Electrode polarization potential is selected via a potentiometer connected to a bipolar reference supply. The voltage source keeps the potential at the platinum electrode equal to the selected potential via a feedback circuit. Electrode current is measured as a voltage drop across resistor $R$. Common mode voltage is eliminated and a DC gain of 50 is supplied by the amplification and balancing circuits. A balance input allows the subtraction of anomalous electrode currents not related to hydrogen concentration and thus provides easy control of the baseline. A low-pass filter is used to eliminate noise due to brain electrical activity and electrical apparatus within the laboratory.

With the electrodes used in these studies, an overall system gain of 50 was used. This yields an output of 5 volts per microampere of electrode current, a value sufficient for the polarograph to be directly connected to a multichannel pen recorder.

Depth electrodes were made of platinum wire (10% iridium, 254 μm in diameter) insulated with glass tubing (Corning 0.3 to 0.6 mm) and heat sealed, with a bare tip of approximately 1 to 2 mm. All electrodes were electroplated in a 5% solution of platinic chloride for 30 seconds with a 1.5V "A" cell.

A 100 ml glass flow chamber was constructed to test the electrodes in vitro. Calibration of the electrodes was unnecessary to determine the cerebral blood flow rate, but their sensitivities were tested after electroplating to obtain a comparable response during the in vivo washout phase. Other variables tested included the response time and linearity of the electrodes as well as the optimal bias potential and specificity of the electrochemical reaction. Hydrogen gas was bubbled through saline in a separatory funnel and the saturated solution was withdrawn with a 25 ml syringe. The mixture was found by gas chromatography to contain approximately 4 μmol of hydrogen in 10 ml of saline and after injection into the flow chamber $10^{-5}$ mol remained in the vicinity of the sensing electrodes for 15 to 18 seconds. Individual polarograms utilizing reference electrodes constructed of stainless steel, nickel-plated brass, or sintered silver/silver chloride were constructed to determine the optimal bias potential for the hydrogen ionization as well as the response to oxygen and carbon dioxide dissolved in saline.

Fourteen rhesus monkeys weighing between 3.5 and 4.5 kg were initially anesthetized with sodium pentobarbital (25

![FIGURE 1](http://stroke.ahajournals.org/)

Functional block diagram of polarographical circuit for measuring hydrogen concentration in tissue with platinum electrodes.
mg per kilogram). The larynx was sprayed with Cetacaine (benzocaine) and the trachea was intubated. A PE-60 catheter was passed transmurally to the aortic arch and was connected to a Statham P23Db transducer for continuous monitoring of mean blood pressure and administration of hydrogen-saturated saline. The femoral vein was cannulated and the central venous pressure was monitored with a Statham P23V transducer. In some animals a 32-gauge teflon-coated platinum wire insulated except for the distal 2 mm was passed into the abdominal aorta through the opposite femoral artery to determine the central aortic levels of hydrogen. The animals were then placed in a Kopf stereotactic head frame, and a burr hole was placed at the inion exposing the torcular. A hollow luicate screw containing a teflon-coated platinum electrode (254 n diameter) was inserted into the torcular for recording average total hemispheric blood flow. The sinus electrode was then led subcutaneously to the posterior thoracic region and access was obtained by a separate stab wound.

Depth electrodes were placed utilizing the stereotaxic coordinates of Snyder and Lee, while cortical electrodes were placed under direct vision. Impedance measurements (table 1) between sensing and reference electrodes were made during passage of electrodes and after final positioning using a General Radio Co. 1650-A impedance bridge. The electrodes were then fixed to the skull with dental acrylic and soldered to a 32 pin contact electrical connector. Transorbital and lateral skull films were taken to provide radiological confirmation of final positioning before the experiments were begun. The electrodes were linked via a matrix board to either of eight separate amplifiers whose output was displayed on a Brush Mark 200 eight-channel recorder, traveling at 0.2 mm per second.

Twenty-four to 48 hours after implantation, the animals were transferred to primate restraint chairs which they tolerated without apparent discomfort. Intermittent cerebral blood flow measurements were carried out for three to five days in the conscious state. Arterial blood gas samples were withdrawn prior to each study. The bolus injection of 10 to 15 ml of saline containing 4 to 6 \(^{\text{\textsuperscript{1}}}\text{mol}\) of molecular hydrogen was recorded as a sharp increase of the current followed by a decay lasting five to seven minutes. The latter values were then used to derive the weighted mean flow as:

\[
F = X \frac{0.693}{t^{1/2}} \quad (100),
\]

while biexponential decays were resolved into fast and slow components after curve stripping and extrapolation of slopes to the initial intercepts. The latter values were then used to determine a separate series of conscious rhesus monkeys.

After serial studies in the awake state local cerebral blood flow studies were repeated under controlled ventilation. Nine animals were ventilated with a mixture of 25% oxygen and 75% nitrous oxide and five animals were given 25 to 35 mg per kilogram sodium pentobarbital. In both groups the levels of analgesia allowed for a feeble corneal reflex.

At the completion of these studies 0.5 ma of current was passed anodally at each electrode for three minutes. The brain was removed and placed in formalin for three days and coronal slices were made for pathological verification of the electrode placement.

**Results**

**ELECTROCHEMICAL CONSIDERATIONS**

Polarograms were developed in the flow model to describe the current generated by the half cell reaction of hydrogen ionization in relation to three different reference half cells (fig. 2). The results for the nickel-plated brass screw indicate a relatively narrow range around which uniform output responses were obtained and lie within a range of values of the bias potential that predicted from the published half cell reactions. When a silver/silver chloride reference was used, a constant current plateau was difficult to achieve over a voltage range of more than 0.1 mV. The measured half cell potential for a platinum/stainless steel cell varies with the particular composition of steel, but is stable for a particular lot of screws. The

![Graph showing polarograms for different materials](image-url)
range of uniform current responses to a platinum/stainless steel cell lies between 0.4 and 0.7 mV (fig. 2).

Using the stainless steel screw as a reference electrode a family of polarograms was constructed to determine the current output with graded increases of hydrogen concentration. In the flow model, at applied bias potentials between +0.4 mV and +0.7 mV, the current flow was linearly related to the hydrogen concentration (fig. 3). In the anesthetized animal a direct relationship between inspired air content of hydrogen and baseline current values was also demonstrated, providing the inspired oxygen content a useful guide to final positioning of the electrodes.

The specificity of the platinum black/stainless steel cell for hydrogen ionization is indicated by the polarogram in figure 4. At bias potentials greater than +0.8 mV or less than —0.1 mV a large current deflection related to the injection itself was noted but sustained deflections, with a typical washout curve, were present only after introduction of hydrogen in saline.

Impedance was determined between reference and sensing electrodes and between pairs of sensing electrodes during implantation. These values were a useful guide to final positioning of the electrodes. When A.C. impedance between two sensing electrodes fell below 2,000 Q, D.C. current flow in tissue made the polarographical circuit difficult to balance. The average impedance values for sensing and reference electrodes after final positioning are given in table 1. The standard deviations, not shown in the table, varied between 9% and 22% of the average. Low impedance values were particularly bothersome between five caudate and thalamic pairs. On postmortem examination these electrodes were seen to have penetrated the lateral ventricles and were in actual contact with ventricular fluid. Impedance increased up to 10% in 32 electrodes and decreased by as much as 23% in 11 electrodes over 48 hours. In 17 electrodes there was no significant change in A.C. impedance.

SLOW BOLUS INJECTION IN CONSCIOUS ANIMALS

Hydrogen-saturated saline (4 to 6 jumol in 10 to 15 ml) was injected over 15 to 20 seconds. At this rate, no significant change in mean blood pressure occurred. Arterial Po, and Pco, values as well as central venous pressure remained stable. Motor activity of the trunk and upper limbs was slightly increased during a total of six injections in two animals, although blood pressure and respiratory rates did not change significantly. In the remainder of the studies, no visible effects of the injection were noted. The difference in blood flow rates when 12 to 14 ^mol in 20 to 25 ml of saline were injected was less than 16%, which is within the percentage error of the method. When volumes greater than 15 ml were used, the prolonged
Relationship between hydrogen concentration and current output for bolus injections in vivo and in vitro indicated by solid lines. Relationship between hydrogen content in inspired air and current recorded indicated by broken line.

injection overlapped the earliest phase of washout, making extrapolation to the onset of desaturation difficult.

CURVE ANALYSIS

The vast majority of washout curves from deep gray nuclei and white matter in conscious monkeys were composed of a single compartment. Most of the multicompartamental studies were derived from cortical electrodes. This is detailed for the various locations in table 2. Initially only 4 of 14 curves from cortical regions were resolved into monoexponential compo-

**TABLE 2**

<table>
<thead>
<tr>
<th>Structure</th>
<th>No. of monoexponential curves</th>
<th>No. of biexponential curves</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conscious</td>
<td>Nitrous oxide</td>
</tr>
<tr>
<td>Cortex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal (+ motor)</td>
<td>48</td>
<td>7</td>
</tr>
<tr>
<td>Parietal (+ sensory)</td>
<td>33</td>
<td>14</td>
</tr>
<tr>
<td>Temporal</td>
<td>42</td>
<td>11</td>
</tr>
<tr>
<td>Occipital</td>
<td>37</td>
<td>15</td>
</tr>
<tr>
<td>Deep gray nuclei</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudate</td>
<td>64</td>
<td>9</td>
</tr>
<tr>
<td>Putamen</td>
<td>75</td>
<td>6</td>
</tr>
<tr>
<td>Amygdala</td>
<td>86</td>
<td>11</td>
</tr>
<tr>
<td>Thalamus</td>
<td>68</td>
<td>18</td>
</tr>
<tr>
<td>Centrum semiovale</td>
<td>107</td>
<td>14</td>
</tr>
<tr>
<td>Pontine tegumentum</td>
<td>91</td>
<td>16</td>
</tr>
<tr>
<td>Total curves</td>
<td>651</td>
<td>121</td>
</tr>
</tbody>
</table>
Polarographical Measurement of Local Cerebral Blood Flow

Specificity of circuit for hydrogen was indicated in vitro by positive and sustained current flow at applied bias potentials around 0.6 mV.

Cortical electrodes were then modified so that the active electrode was less than 1 mm in length. Following this 160 of 183 curves from the cortex were noted to conform to a monophasic slope and only these data were included in tables 2 and 3.

Local Cerebral Blood Flow

Cerebral blood flow rates in each of 12 structures in the conscious rhesus monkey are given in table 3. These are mean values of both monoexponential and biexponential washout curves. Only those measurements from electrodes with postmortem confirmation of position were included in the final tabulations. Higher mean flow values were derived from recordings in motor (86.2 ± 2.6 ml/100 gm per minute) cortex than from the mean (75.6 ± 3.1 ml/100 gm per minute) value for all recordings in the prefrontal cortex. The mean blood flow of the sensory cortex (92.5 ± 3.5 ml/100 gm per minute) was not significantly greater than the mean blood flow of the parietal cortex (80.4 ± 14.1 ml/100 gm per minute). There were no significant differences in blood flow values between other cortical areas with individual flow rates ranging between 63.2 and 160 ml/100 gm per minute. The slow compartment flow rates recorded from biexponential cortical curves (mean 20.6 ± 5.6 ml/100 gm per minute) did not differ significantly from that estimated from studies of the centrum semiovale. There was no consistent difference between right and left hemispheres for either cortical or subcortical blood flow values, in individual experiments or in the pooled data. Standard deviations

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and standard errors of the mean for individual structures are given in table 3.

The mean local blood flow rates for the deep gray nuclei ranged between 57.6 ± 3.8 ml/100 gm per minute and 69.2 ± 3.4 ml/100 gm per minute. Mean values for each of the four nuclear masses studied are given in table 3. Values for the centrum semiovale measured at a standard stereotaxic location (A 6.0, R, L 7.5 H + 6.5) varied between 14 and 26 ml/100 gm per minute and showed a variation of less than 12% on serial studies in the same animal.

**AREAS OF HYPEREMIA**

Ten electrodes consistently recorded flow values over 140 ml/100 gm per minute. On postmortem study, seven of these sites were found to be adjacent to either arterioles or areas of visible hyperemia. Three of the seven electrodes were in the amygdala and all had biexponential washout curves. The mean half-time for the initial component was 25 seconds, corresponding to a flow of 166 ml/100 gm per minute. The second component had a mean half-time of 1.13 minutes, corresponding to a flow of 61 ml/100 gm per minute and 69.2 ± 3.4 ml/100 gm per minute. Mean values for each of the four nuclear masses studied are given in table 3. Values for the centrum semiovale ranged between 14 and 26 ml/100 gm per minute and showed a variation of less than 12% on serial studies in the same animal.

The mean local blood flow rates for the deep gray nuclei were 77.0 ± 2.6 ml/100 gm per minute and the mean blood flow value for the slow compartment was 24.0 ± 0.7 ml/100 gm per minute (table 4). Average hemispheric blood flow for the structures drained by the torcular herophili was 56.0 ± 12 ml/100 gm per minute.

**TABLE 4**

<table>
<thead>
<tr>
<th>Average Total Cerebral Blood Flow Measured From a Vascular Electrode in the Torcular Herophili (ml/100 gm per minute)</th>
<th>Fg</th>
<th>Fw</th>
<th>F</th>
<th>1/L + L</th>
<th>II/II + IIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>77.0</td>
<td>24.0</td>
<td>56.0</td>
<td>52.5</td>
<td>47.5</td>
</tr>
<tr>
<td>SD</td>
<td>13.2</td>
<td>* 3.0</td>
<td>± 7.5</td>
<td>± 5.3</td>
<td>± 3.6</td>
</tr>
<tr>
<td>SE</td>
<td>2.6</td>
<td>0.7</td>
<td>12</td>
<td>2.4</td>
<td>0.9</td>
</tr>
</tbody>
</table>

**BLOOD FLOW STUDIES UNDER NITROUS OXIDE ANESTHESIA**

A mixture of 75% nitrous oxide and 25% oxygen was administered by endotracheal tube to 9 of 14 animals. These animals were fully paralyzed with intravenous d-tubocurarine. Oxygen concentration in the inspired mixture was maintained between 20% and 25%. The mean arterial PO2 was 140 ± 7 mm Hg, the mean arterial PCO2 was 38 ± 4 mm Hg and mean arterial PO2 was 110 ± 16 mm Hg. The reduction in cortical flow values was not significant. Blood flow in the caudate nucleus was reduced from 64.6 ± 2.4 to 57.2 ± 1.9. This is significant at the 0.05 level only. There was no significant reduction of flow in other deep gray nuclei, centrum semiovale or pontine tegmentum (table 3).

**BLOOD FLOW STUDIES UNDER PENTOBARBITAL ANESTHESIA**

The depth of anesthesia was adjusted to maintain pupillary reaction to light stimulus. In this group the mean arterial Po2 value was 114 ± 19 mm Hg, the mean arterial PCO2 value 37.5 ± 4 mm Hg and the mean pH 7.388 ± 0.051 pH units. Local cerebral blood flow values in specific areas were significantly depressed in all cortical areas studied except for the occipital cortex. The small decrease noted in the putamen is not significant. Blood flow in the white matter of the centrum semiovale was not significantly depressed by pentobarbital (table 3).

**Discussion**

Most current isotopic techniques for measuring cerebral blood flow in regional, microregional and local areas of interest are limited in resolution because of scatter and distortion considerations. Autoradiographical methods provide the highest degree of resolution but are limited by the number of determinations which can be made at the time of sacrifice. The application of polarographical techniques to the study of microregional blood flow rates provides the capability for repeated recording from areas whose size is related to the diameter of the open electrode tip. A variation between serial measurements of 3% to 16% was found under steady state conditions. This degree of reproducibility is also dependent to some degree on the size of the electrodes and the "field of view" of each electrode. Leniger-Follert and Lubbers felt that the variability of flow values,
POLAROGRAPHICAL MEASUREMENT OF LOCAL CEREBRAL BLOOD FLOW

utilizing electrodes less than 100 n in diameter, was a reflection of the flow currents in the capillary bed. These recordings contrast with the more constant flow in arteriolar beds seen by larger electrodes. Utilizing 254 n diameter platinum electrodes,26 flow is probably measured within a cylinder of tissue whose volume is less than 1 mm³.

The advantages of the hydrogen dilution technique for measuring blood flow in the unanesthetized animal were recognized by Haining in his studies in the rat.18 Compared with heat clearance techniques this method is quantitative and allows measurement in deep cerebral structures. Blood flow may be recorded at several sites simultaneously, the only limitation being the topographical arrangement on the vertex of the skull and the number of channels which can be accommodated in the amplifiers and recording systems.

In vitro studies using the glass chamber model were necessary to study the specificity, optimal bias and linearity of the electrochemical reaction. Distortion of the contents of the flow chamber by injection of distilled water, or injection of either saline, oxygen-saturated saline or carbon dioxide-saturated saline elicited a potential change whose amplitude was approximately one-third of that produced by a similar injection of hydrogen-saturated saline. The calculated maximal current output of the reaction of 4 × 10⁻¹ coulombs is 0.1 amp. This is far in excess of the output of 2 to 7 ma seen experimentally in the glass chamber model. Diffusion gradients as well as the passage of a large volume of nonionized hydrogen through the flow chamber reduced the availability of hydrogen to the electrodes. Furthermore, while a positive bias of 0.65 V produced the optimum bias for maximal current flow, the half cell reaction for platinum/stainless steel is variable depending on the particular composition of the stainless steel.

The problem of recirculation of hydrogen discussed by both Meyer1 and Pasztor18 was largely obviated by the bolus injection of hydrogen. The former used a bolus injection of hydrogen-saturated saline into the lingual artery of the monkey. This route is appropriate for unilateral studies but our technique utilized injection at the aortic arch to provide washout from both hemispheres for comparison. Objections to the use of a central aortic bolus were raised by Hutten et al.,27 who found that the curve analysis for 85-Krypton was complicated by dispersion of the bolus at the time it reaches the hemisphere. Since the initial pen deflections were rapid and indicative of a bolus arrival of hydrogen at the electrodes, this is probably not a serious criticism of our technique. The degree to which the slower bolus injection contributed to early recirculation of hydrogen was assessed by an aortic electrode. The arterial desaturation demonstrated a mean half-time for washout of 37 seconds. Meyer31 reported an arterial desaturation that takes many minutes after inhalation of hydrogen, while Pasztor and others32 reported a half-time of 28 seconds. The latter authors recommended neglecting the first 40 seconds in the washout curve in deriving the slope of the first component.

The local blood flow values which we obtained for the cerebral cortex in conscious animals are higher than those reported during anesthesia by other authors.1-16-18 Using the polarographical technique in chloralose anesthetized and paralyzed baboons, Symon et al.28 obtained local cortical blood flow values ranging from 21 ml/100 gm per minute to 94.5 ml/100 gm per minute, with mean values ranging from 48.2 ± 12.0 ml/100 gm per minute to 54.4 ± 19.0 ml/100 gm per minute. To analyze both monoexponential and biexponential decays before and after middle Ilerbral artery occlusion flows were calculated from the two-minute flow index (TMFI) after the first 40-second washout. The latter was excluded because of arterial recirculation of hydrogen but should have a more significant relative effect on the TMFI than on cerebral blood flow calculated from either stochastic or multicompartmental analyses.23 The flow values which we obtained in cerebral cortex, however, are lower than the results reported in unanesthetized cat by Landau et al.,10 using the C¹ antipyrine technique. We were able to confirm in rhesus monkeys the significant difference which they noted between sensory-motor and association cortex.

With a rapid bolus injection or in a hyperemic brain, the fast component is preferentially saturated.22 A slower saturation such as is achieved with inhalation results in a more even saturation of both flow compartments. The consistent although incomplete degree of saturation of the slow compartment by our modified bolus injection is illustrated by the relative constancy of the initial weight of the slow compartment (table 4). Aukland22 originally pointed out that an even saturation of both slow and fast compartments can be achieved with a prolonged intra-aortic infusion of hydrogen-saturated saline.

The value of studies in conscious animals is demonstrated by the artifacts superimposed when anesthetics are used. Our studies indicate that the changes in perfusion rates induced by pentobarbital anesthesia are most pronounced in structures with a more rapid blood flow rate. The effects of these agents on cerebral blood flow and metabolism have been summarized in reviews by Sokoloff,29 Smith and Wollman30 and Fink and Haschke.31 In man 70% nitrous oxide reduced CMRO₂ by 15% with no significant effect on flow.30,32 CMRO₂ was decreased by 2% in another study32 and by 23% in two others.33,34 The common complaints of paresthesias and lightheadedness associated with the administration of 15% nitrous oxide for clinical cerebral blood flow studies also suggest an influence on cerebral metabolism. Barbiturate anesthesia, on the other hand, has a primary
effect on cerebral functional activity with a resultant decrease in cerebral metabolic activity. The refractory period of the primary evoked cortical response as well as the latent period for the secondary response are both increased, while the cortical after-effect, normally mediated by recurrent thalamocortical pathways, is suppressed. The decreased CMRO$_2$ noted after addition of barbiturates is not secondary to circulatory insufficiency. Instead this reflects the reduced demand for oxidative energy associated with the depression of functional activity, which may be secondary to the inhibition by these anesthetic agents of synaptic transmission and neuronal interaction.

When blood flow is measured in very discrete volumes of brain tissue by polarographical techniques or by the radiotracer methods of Kety et al., the vasodilator effects of barbiturates are dramatic. These effects are more pronounced relative to measurement which employ considerably more averaging of multiple compartments and functionally unrelated areas. This sensitivity to changes in the steady state measurements indicates that attention to the level of consciousness and the presence of anesthetic agents is important when cerebral blood flow is measured by the polarographical technique. A large number of studies of both flow and metabolism have employed anesthetic levels of barbiturate. The decreased metabolic requirements induced by barbiturates may in fact underlie the electrophysiological recovery after prolonged ischemia noted by Hossmann and Sato.

The measured reductions of local blood flow found in our studies reflect upon the induced changes in metabolic requirements and represent a protective effect of barbiturates. These are important considerations when evaluating cerebral nutritional deficits occurring during stroke.

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