An Experimental Model of Brain Ischemia Combining Hypotension and Hypoxia

BY FRANK M. YATSU, M.D., PETER LINDQUIST, AND CHARLES GRAZIANO

Abstract: An Experimental Model of Brain Ischemia Combining Hypotension and Hypoxia

A variety of experimental models for cerebral ischemia are currently available, but none are entirely satisfactory. We are reporting a model which combines hypotension, produced by intravenous Arfonad, with hypoxia, produced by respiring 4% oxygen. Rabbits used are awake but paralyzed with succinylcholine and ventilated mechanically. The electroencephalogram (EEG) is monitored with durally implanted electrodes. Onset of an isoelectric EEG ensues in 4.5 ± 0.7 minutes in 17 rabbits studied and is used to measure the degree of ischemic insult. After three minutes of an isoelectric EEG, circulatory restoration is followed by complete functional recovery. After five minutes of an isoelectric EEG, rabbits do not recover or show neurological deficits such as limb weakness. The potential effects of systemic ischemia on these animals are minimized because of the rapid onset of ischemic brain damage. Examination of arterial blood gases, pH, platelets, various organs histologically, and the distribution of carbon-particles in the intracerebral circulation reveals that systemic factors are minimal. Moderately delayed onset of cortical EEG activity and the presence of motor impairment or an inability to respire satisfactorily after extubation indicates that the brunt of ischemic insult is upon brain. Our model has the advantages of simplicity and predictability and offers the opportunity to assess functional impairment after graded degrees of cerebral ischemia. We conclude that our model of cerebral ischemia produced by hypotension and hypoxia is a reasonable alternative to existing methods.

Additional Key Words

EEG activity impaired cerebral circulation cerebral ischemia

Introduction

Cerebral ischemia results from impaired cerebral circulation and is accompanied by functional derangement of brain. Although no model satisfactorily duplicates human cerebral ischemia, a variety of experimental models have been used, including decapitation, hemorrhagic shock, cross-perfusion technique and vascular ligation or embolization.

The experimental model we are reporting produces cerebral ischemia by combining systemic hypotension with hypoxia to reduce obligate brain substrates, i.e., glucose and oxygen. This model, which is relatively simple, affects primarily the brain, permits evaluation of neurological status following circulatory restoration after graded periods of ischemia, and provides the potential capability of identifying biochemical alterations during the reversible and irreversible phases of ischemic brain damage.

Methods

The experiments were performed on 17 random bred New Zealand white rabbits weighing 3.1 to 4.5 kilograms. Six were subjected to moderate cerebral ischemia, six to severe cerebral ischemia, and five were control animals.

The experimental procedure can be divided into five periods: base, hypotensive, hypotensive and hypoxic, ischemic, and recovery.

BASE

During the base period, the rabbits were given intravenous cyclohexylamine (ketamine), 15 mg per kilogram, and then intubated with a cuff endotracheal tube. After intubation, they were paralyzed with intravenous succinylcholine (10 mg) and mechanically ventilated on a Harvard pump with 75 to 90 cc per stroke at 25 to 35 breaths per minute. Additional succinylcholine was administered in 5 mg increments throughout the preischemic period, resulting in an average total dosage of 7 mg per kilogram. A small amount of oxygen was introduced through the respirator to ensure that the blood would be fully oxygenated. End-tidal CO₂ was monitored by a Beckman Medical Gas Analyzer, Model LB-1 (Beckman Instruments, Inc., Spinco Division, Palo Alto, California). The rate of respiration was adjusted periodically in the base period to maintain a constant expired CO₂ in the range of 4.9% to 5.2% CO₂. Arterial Pₐ, Pₒ₂, and pH were monitored by a Radiometer Model PHA927 with Pₒ₂ electrode type E5046, Pₒ₂ electrode type E5036, and pH glass electrode type E5021 (Radiometer, 72 EMDRUPVE, Copenhagen NY, Denmark). Cortical electrodes were used to record the electrical potential of the cortex. Stainless-steel screw electrodes were implanted parasagittally into the cranial dura 1 cm apart at the level of

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the anterior motor and posterior sensorimotor cortex. The stainless-steel electrodes displayed less than 10,000 ohm resistance and the electroencephalogram (EEG) was recorded with a standard 8-channel Grass Electroencephalograph — Model 5 (Quincy, Massachusetts), which also recorded the electrocardiogram (EKG). Resting EEG activities were comparable to those previously reported. The femoral artery was catheterized for constant blood pressure recording through a Statham-P23Db transducer and visual readout utilizing the Electronics for Medicine PR-7 (White Plains, New York). The femoral artery catheter allowed for the collection of blood for gases and pH. Body temperature was recorded by a rectal thermometer (Yellow Springs Instruments, Yellow Springs, Ohio) and was maintained by a heating pad. All operative procedures utilized local anesthesia (0.5% xylocaine) to control pain for the paralyzed rabbit. Wound areas were reinfiltreated every 30 minutes to assure proper anesthetic effect. The operative procedures were performed while the animal was restrained on an adjustable tilt table.

HYPOTENSION

During the hypotensive period, the rabbit was tilted head-up at 30°, and trimethaphan (Arfonad) was given intravenously in 5 to 10 mg increments until the mean arterial blood pressure stabilized at 20 to 30 mm Hg. The hypotensive level was reached in 2.1 ± 0.4 minutes.

HYPOTENSION AND HYPOXIA

Once the blood pressure stabilized at 20 to 30 mm Hg, 4% oxygen with 96% nitrogen was given through the Harvard pump. Trimethaphan was administered as above during this period to compensate for two physiological responses: hypertension and increased cardiac output. (The average total dosage of trimethaphan throughout the experiment was 7 mg per kilogram.) The onset of an isoelectric EEG after the induction of hypotension was an average 4.5 ± 0.7 minutes in all animals, or 2.3 ± 0.3 minutes after the initiation of 4% oxygen. An isoelectric EEG is defined as electrical activity of less than two microvolts’ amplitude. In all cases, the isoelectric point was easily determined; the demarcation between electrical activity and no electrical activity was quite distinct.

ISCHEMIA

The period of ischemia was defined as the time that an isoelectric EEG supervened. The isoelectric EEG persisted as long as 4% oxygen was administered, and since the blood pressure remained below 30 mm Hg, additional trimethaphan was not required. The severity of the ischemic insult was arbitrarily equated to the duration of the isoelectric EEG before 100% oxygen therapy was begun. In the control rabbits, 100% oxygen was administered as soon as the EEG became isoelectric, with a mean time interval of 0.30 ± 0.03 minute from the onset of the isoelectric EEG to the administration of 100% oxygen. Of the two remaining groups of rabbits, one group was subjected to moderate ischemia with the EEG isoelectric for three minutes before the introduction of 100% oxygen, and the last group was subjected to severe ischemia, i.e., five-minute isoelectric EEG before 100% oxygen.

During the three-minute and five-minute periods of isoelectric EEG, the arterial blood pressure typically fell and the cardiac rate decreased by as much as 50%. In order to maintain the blood pressure between 15 and 20 mm Hg, the tilt table was frequently brought to the horizontal or the Trendelenburg position (head down) since the arterial blood pressure may drop to 10 mm Hg. In all animals, the body temperature slowly declined despite attempts to stabilize it.

RECOVERY

In the five-minute ischemic group of animals, following administration of 100% oxygen, pressors (adrenaline, 0.33 mg, and/or isoproterenol-HCl [Isuprel], 0.03 mg) were required to restore arterial blood pressure in all rabbits. This measure, to restore blood pressure promptly, was taken to insure adequate cerebral perfusion. To facilitate recovery from the curare-like effects of trimethaphan, all rabbits were given neostigmine (0.25 mg) and atropine (0.1 mg). In the control group, the EEG activity returned 0.3 ± 0.08 minute after 100% oxygen was given. For the three-minute ischemic group the EEG activity returned 1.18 ± 0.38 minutes and for the five-minute ischemic group 14.9 ± 0.9 minutes after 100% oxygen. Upon return of normal respiratory movement, the rabbits were exubated and placed in an incubator. The control and three-minute ischemic animals were removed from the respirator on an average of 0.5 to 1.0 hour after the ischemic insult, whereas the five-minute ischemic rabbits required respiratory assistance for two to three hours after ischemia. Careful and attentive care in the postischemic or recovery period was uniformly maintained for each animal.

CARBON PARTICLE INFUSION AS AN INDICATOR OF CEREBRAL BLOOD FLOW

Two rabbits, not used for the ischemic studies, weighing 3.0 and 3.4 kilograms were subjected to five minutes of cerebral ischemia, after which a carbon particle suspension was administered through the jugular vein. The carbon particle suspension was prepared from commercial “Higgins” India ink containing 80 mg per milliliter of carbon. The dose was 16 mg/110 gm, which was diluted 1:1 with saline and administered over a 30-second interval at the end of the five minutes of ischemia while the rabbits were hypotensive and hypoxic. The animal was killed and the brain was fixed in neutral 10% formalin for several days. Seven micron coronal sections were stained with nuclear fast red (Kernechturbin).

PLATELET STUDIES

Platelet counts were performed by Dr. Mervyn Sahud (Assistant Professor of Medicine, University of California School of Medicine, San Francisco, California), with a slight modification of standard techniques. The slow sedimentation rate of rabbit red blood cells required a 2:1 dilution of whole blood instead of the usual 1:1 dilution (two parts polyvinylpyrrolidone [PVP] to one part whole blood). The platelet studies were done in a Coulter Counter Model ZBI and Coulter Channelyzer, Coulter Electronics Inc., Hialeah, Florida.

Histological sections (hematoxylin and eosin) were made from the organs of five of the five-minute ischemic animals. The organs studied were lung, heart, liver, kidney and adrenal glands. Only three of the brains were obtained from the control group, the EEG activity returned 0.33 ± 0.08 minute after 100% oxygen was given. For the three-minute ischemic group the EEG activity returned 1.18 ± 0.38 minutes and for the five-minute ischemic group 14.9 ± 0.9 minutes after 100% oxygen. Upon return of normal respiratory movement, the rabbits were exubated and placed in an incubator. The control and three-minute ischemic animals were removed from the respirator on an average of 0.5 to 1.0 hour after the ischemic insult, whereas the five-minute ischemic rabbits required respiratory assistance for two to three hours after ischemia. Careful and attentive care in the postischemic or recovery period was uniformly maintained for each animal.

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Results

Results of our studies are given in tables 1 through 3 and in figures 1 through 3. It is noted in table 1 that the time it took to achieve a stable level of arterial hypotension and an isoelectric EEG after the introduction of 4% oxygen were not significantly different in the three experimental groups. Although the duration of hypotension averaged 3.3 minutes in the five-minute ischemic rabbits, compared to 1.5 minutes for the other two groups, it was not statistically significant because the range was sufficiently large. Similarly, the time required to regain arterial blood pressure to baseline levels was not significantly different in the three experimental groups. Mean recovery time for blood pressure was 3.1 minutes for the five-minute ischemic animals, but again, the range of values made it statistically insignificant. Likewise, return of the end-tidal CO$_2$ occurred at similar time periods while the volume and rate of respiration were maintained. EEG recovery-time was a significantly different parameter in the five-minute ischemic rabbits. In addition to the late onset for this activity, the EEG tended to be less well organized with increased amounts of slow-wave activity. This result implies functional impairment of brain.

Arterial blood studies are given in table 2. A slight increase in arterial P$_{A\text{CO}_2}$ occurred in the three-minute ischemic rabbits prior to the onset of hypotension. This unexpected finding may be due to CO$_2$ retention while undergoing intubation. The only other significant alteration in arterial blood studies was

<table>
<thead>
<tr>
<th>No. of rabbits</th>
<th>Control</th>
<th>3-minute Ischemia</th>
<th>5-minute Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preischemic and ischemic periods</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(A) Hypotension</td>
<td>1.50 ± 0.30</td>
<td>1.50 ± 0.20*</td>
<td>3.30 ± 1.00*</td>
</tr>
<tr>
<td>(B) Hypotension and hypoxia</td>
<td>2.10 ± 0.60</td>
<td>2.10 ± 0.30*</td>
<td>2.70 ± 0.70*</td>
</tr>
<tr>
<td>(C) Ischemia</td>
<td>0.30 ± 0.03</td>
<td>3.00 ± 0</td>
<td>5.00 ± 0</td>
</tr>
<tr>
<td>Recovery period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(D) Blood pressure restoration</td>
<td>1.22 ± 0.36</td>
<td>1.92 ± 0.55*</td>
<td>3.10 ± 1.00*</td>
</tr>
<tr>
<td>(E) End-tidal % CO$_2$</td>
<td>1.83 ± 0.77</td>
<td>1.22 ± 0.35*</td>
<td>1.90 ± 0.50*</td>
</tr>
<tr>
<td>(F) EEG electric activity</td>
<td>0.33 ± 0.08</td>
<td>1.18 ± 0.38*</td>
<td>14.90 ± 0.90*</td>
</tr>
</tbody>
</table>

A = Duration of hypotension produced by I.V. trimethaphan (Arfonad).
B = Duration of hypotension and hypoxia produced by I.V. trimethaphan and 4% oxygen before the onset of an isoelectric EEG.
C = Duration of ischemia following onset of an isoelectric EEG while hypotensive and hypoxic.
D = Interval to blood pressure recovery (to preischemic or base levels) after the addition of 100% oxygen.
E = Interval to end-tidal % CO$_2$ recovery (to preischemic or base levels) after the addition of 100% oxygen.
F = Interval to EEG activity after the addition of 100% oxygen.

* = P > 0.05.
† = P < 0.001.

P = Level of significance between the control group and either the three-minute or five-minute ischemic groups.
**TABLE 2**

**Blood Gases and pH During Periods of Preischemic, Ischemic, and Postischemic Recovery**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>3-minute ischemia</th>
<th>5-minute ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of rabbits</td>
<td>5</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>(A) Base</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.41 ± 0.02</td>
<td>7.41 ± 0.02*</td>
<td>7.39 ± 0.01*</td>
</tr>
<tr>
<td>Pa CO2 (mm Hg)</td>
<td>40.00 ± 2.00</td>
<td>45.00 ± 3.00*</td>
<td>43.00 ± 2.00*</td>
</tr>
<tr>
<td>Pa O2 (mm Hg)</td>
<td>85.00 ± 9.00</td>
<td>80.00 ± 8.00*</td>
<td>89.00 ± 4.00*</td>
</tr>
<tr>
<td>(B) Prehypotensive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.39 ± 0.03</td>
<td>7.43 ± 0.02*</td>
<td>7.38 ± 0.01*</td>
</tr>
<tr>
<td>Pa CO2 (mm Hg)</td>
<td>37.00 ± 3.00</td>
<td>46.00 ± 3.00†</td>
<td>42.00 ± 3.00*</td>
</tr>
<tr>
<td>Pa O2 (mm Hg)</td>
<td>196.00 ± 16.00</td>
<td>216.00 ± 27.00*</td>
<td>205.00 ± 24.00*</td>
</tr>
<tr>
<td>(C) Ischemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.42 ± 0.03</td>
<td>7.51 ± 0.03*</td>
<td>7.44 ± 0.05*</td>
</tr>
<tr>
<td>Pa CO2 (mm Hg)</td>
<td>31.00 ± 2.00</td>
<td>37.00 ± 4.00</td>
<td>28.00 ± 3.00*</td>
</tr>
<tr>
<td>Pa O2 (mm Hg)</td>
<td>24.00 ± 3.00</td>
<td>20.00 ± 1.00*</td>
<td>24.00 ± 2.00*</td>
</tr>
<tr>
<td>(D) Postextubation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.43 ± 0.02</td>
<td>7.43 ± 0.02*</td>
<td>7.33 ± 0.04†</td>
</tr>
<tr>
<td>Pa CO2 (mm Hg)</td>
<td>36.00 ± 3.00</td>
<td>37.00 ± 2.00*</td>
<td>43.00 ± 3.00*</td>
</tr>
<tr>
<td>Pa O2 (mm Hg)</td>
<td>125.00 ± 36.00</td>
<td>161.00 ± 32.00*</td>
<td>167.00 ± 19.00*</td>
</tr>
</tbody>
</table>

A = Arterial blood sample taken before any operative procedure.
B = Arterial blood sample taken immediately before administration of I.V. trimethaphan.
C = Arterial blood sample taken during ischemic period. For the control, sample was taken immediately after EEG became isoelectric; for three-minute ischemic group, sample was taken 1.5 minutes after EEG became isoelectric; and for five-minute ischemic group, sample was taken 2.5 minutes after the onset of an isoelectric EEG.
D = Arterial sample taken after extubation.

Values are means ± SEM.

*P > 0.05.
†P < 0.05.

P = Level of significance between the control group and either the three-minute or five-minute ischemic groups.

Postextubation acidosis; the five-minute ischemic rabbits developed mild arterial acidosis to pH 7.33 ± 0.04.

Studies on platelet counts are given in table 3. Note that there is an absence of any dramatic decrease in circulating platelets during ischemia. In addition, there was no evidence for the recruitment of new platelets as reflected in the percent of large platelets, determined by the Coulter Channelizer. For example, the range of large platelets in control animals was 12% to 22% during baseline and 14% to 24% after extubation; in three-minute ischemia, it was 19% to 39% during baseline and 17% to 37% after extubation; and in five-minute ischemia it was 23% to 29% during baseline and 19% to 23% after extubation.

Figures 1 through 3 graphically depict the changes in mean arterial blood pressure and end-tidal CO2 with the 95% confidence limits on vertical bars. Of note is the relatively uniform response of animals from the three experimental groups.

Body temperature decreased slightly in all animals, but there was no statistical difference between the three groups. The mean temperature drop in the control group was 0.2 ± 0.07°C, while the three-minute ischemic group was 0.5 ± 0.1°C and the five-minute group was 0.5 ± 0.08°C.

**TABLE 3**

**Circulating Platelets Before and After Ischemia**

<table>
<thead>
<tr>
<th></th>
<th>Baseline platelets/mm³ (±10⁶)</th>
<th>Postextubation platelets/mm³ (±10⁶)</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of rabbits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3</td>
<td>394 ± 12</td>
<td>371 ± 54</td>
</tr>
<tr>
<td>Three-minute ischemia</td>
<td>3</td>
<td>419 ± 13</td>
<td>341 ± 58</td>
</tr>
<tr>
<td>Five-minute ischemia</td>
<td>2</td>
<td>368 ± 86</td>
<td>388 ± 56</td>
</tr>
</tbody>
</table>

Values = mean ± SEM.
MEAN ARTERIAL BLOOD PRESSURE AND MEAN END-TIDAL CO₂
DURING 3 MINUTE ISCHEMIA

POSTISCHEMIC STATUS
All of the control animals were subjected to momentary loss of EEG activity; following extubation, each of these five animals showed rapid recovery with no discernible neurological deficits. Ventilation, posture and hopping were normal. Similarly, rabbits subjected to three minutes of an isoelectric EEG were normal in all respects.

All the animals experiencing five minutes of an isoelectric EEG displayed marked impairment of function which appeared to be primarily neurological. Two animals could not be extubated because of poor voluntary respiration and they were killed two and one-half and three hours after the ischemic insults. Three rabbits could be satisfactorily extubated but showed marked neurological impairment such as an inability to right themselves or hop and these animals died 5, 12 and 40 hours after extubation. The sixth animal survived beyond 72 hours but showed persisting inability to right itself and hop normally.

Histological examinations of the brain, lungs, heart, kidney, liver, and adrenal glands in five rabbits dying or killed after five minutes of ischemia showed no significant abnormalities. Specifically, there were no light microscopic evidences for ischemic cell damages, shock lung or disseminated intravascular coagulation. The relatively short time period between the ischemic insult and death or sacrifice may account for the absence of reactive neuronal and glial changes in areas corresponding to functional brain impairment.

Discussion
In 1836 Astley Cooper first reported on the experimental production of cerebral ischemia. In his study, the carotid and/or vertebral arteries in dogs
and rabbits were ligated, and detailed observations were made on the degrees of neurological impairment produced. Since these pioneering studies, various experimental methods for the production of cerebral ischemia have been employed, but each technique has both advantages and limitations. For example, many biochemical studies have relied upon decapitation, but unfortunately this technique does not allow assessment of reversibility. Another technique is vascular occlusion, such as the ascending aorta or the middle cerebral artery. The advantage of this technique is its similarity to thrombotic strokes and the production of neurological impairment as well as its reversal following circulatory restoration. Disadvantages have been requirements for elaborate surgical instrumentation, inability as yet to identify the transition period between reversible and irreversible ischemic damage, and uncertainty of quantitating the degree of local ischemia since collateral circulation variably restores perfusion.

The purposes of our model of cerebral ischemia are twofold: (1) to provide a relatively simple and reproducible model which would satisfy the neurochemical concomitants of ischemia, namely a reduction in the obligate brain substrates, oxygen and glucose, and (2) to provide a model in which functional impairment can be evaluated following graded degrees of cerebral ischemia. The first purpose was accomplished by combining both systemic hypotension and hypoxia to induce global cerebral ischemia. The second purpose was accomplished by restoring the circulation (blood pressure and oxygen) and allowing recovery. The effects of hypoxia and of ischemia appear to have separate effects on whole brain metabolism and particularly on the regulation of cerebral blood flow. However, the critical metabolic effect of ischemia on a cellular level results from both glucose and oxygen deprivation.

In our model, the duration of an isoelectric EEG is used to quantitate the degree of cerebral ischemia. Loss of cortical electrical activity does not imply critical degrees of ischemia, hypoxia or resulting damage since evidences indicate that loss of electrical activity precedes changes in energy state.
Nevertheless, an isoelectric EEG offers a measurable physiological effect of cerebral ischemia. Reduced cerebral blood flow or ischemia must occur during periods of hypotension and hypoxia preceding the onset of an isoelectric EEG, but the similar duration of these periods in our three experimental groups does not detract from using an isoelectric EEG as a measure of ischemic insults. An isoelectric EEG was induced in the same manner in all rabbits, including the control group. Once an isoelectric EEG was obtained in the control group, circulation was immediately restored with a concomitant administration of 100% oxygen. The moderate and severe ischemic insult groups underwent three-minute and five-minute periods, respectively, of isoelectric EEG before restoration of circulation. As indicated in table 1 (columns A and B), all rabbits developed a rapid and uniform onset of an isoelectric EEG following induction of hypotension followed by hypoxia. Circulation restoration (columns D and E) also was rapid and uniform in all rabbits.

As shown in table 2, in the moderately ischemic group there was a mild elevation of the $P_{aCO_2}$ representing $CO_2$ retention following intubation and prior to hypotension. However, this group is unassociated with significant alterations of arterial pH, $P_{aO_2}$ or $P_{aCO_2}$ during or following ischemia when compared to control rabbits. In the severely ischemic group there was a significant alteration in blood pH after the ischemic insult. The arterial pH fell to 7.33 ± 0.04, which might be expected from the sustained ischemia and resulting lactic acidosis.

One significant alteration between the three groups of rabbits was a delay in the occurrence of detectable EEG activity (table 1). This particular finding of delayed electric recovery in the five-minute ischemic group suggests that the brunt of the hypotension-hypoxia insult is primarily upon the brain, since other measurable parameters readily returned to normal.

Because the ischemic insult is of short duration, several potential complications of systemic hypotension and hypoxia are avoided in our preparation. These complications, which may affect cerebral function and the outcome of the experimental model, include systemic acidosis, disseminated intravascular coagulation, shock lung and a selective "watershed" effect on the microcirculation secondary to hypotension.

A mild systemic acidosis seen following five minutes of an isoelectric EEG with a pH drop to 7.33 ± 0.04 would not be expected to impair severely cerebral function since Siesjö has reported that severe degrees of intracellular and extracellular acidosis produced by hypercapnia were not associated with brain impairment.

Disseminated intravascular coagulation is precipitated by sustained hypotension or shock and may cause both cerebral and systemic dysfunction due to platelet thrombi formation. No evidence of disseminated intravascular coagulation was seen histologically in our model and, in addition, platelet counts (table 3) and a determination of their size showed no evidence of consumption coagulopathy. "Shock lungs" is precipitated by sustained shock or hypotension and results in pulmonary atelectasis, transudation, and congestion, but was not seen in our animals with severe ischemia. The absence of disseminated intravascular coagulation and "shock lung" is probably due to the short duration of systemic ischemia.

The possibility of affecting primarily the "watershed" area in our model cannot be excluded since there was no histological evidence of ischemic damage and regional cerebral blood flow studies were not performed. However, functional impairment occurring both in the hindlimbs and forelimbs instead of the forelimbs alone suggests a generalized effect rather than a localized one at the "watershed." Results of intravenous injection of carbon particles over a 30-second period following a five-minute isoelectric EEG showing diffuse distribution of carbon particles further support this conclusion.

It is concluded from our study that combined systemic hypotension and hypoxia complement existing methods of experimental cerebral ischemia. Our model is relatively simple technically and provides the ability to create graded degrees of severe, global cerebral ischemia plus the opportunity to evaluate cerebral recovery. Moreover, the relatively rapid time-course for irreversible ischemic brain damage resembles the ischemic vulnerability of brain seen clinically. This resemblance suggests that neurochemical changes and pharmacological manipulations in our model may have direct relevance to patients with severe cerebral ischemia.

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CORRECTION

An error appeared in the abstract of the article “The Relationship of Regional Cerebrovascular CO₂ Reactivity to Blood Pressure and Regional Resting Flow” by Robert H. Ackerman, M.D., which appeared in STROKE, volume 4, page 725 (September-October) 1973. The following is the corrected abstract.

Cerebrovascular CO₂ reactivity (the change in cerebral blood flow per mm Hg change in PaCO₂) is shown to be directly related to resting flow and inversely related to blood pressure for regional as well as for mean CBF data. Both regional and mean CO₂ reactivity therefore are proportional to the ratio of resting flow to blood pressure. This ratio is the reciprocal of resistance and may be called conductance. When regional CO₂ reactivity for 428 cerebral areas is plotted against an approximation of regional conductance, the data describe a positive linear relationship similar to those found when mean CO₂ reactivity is plotted against mean conductance. These relationships can be demonstrated whether CO₂ reactivity is calculated with specific or percent change in flow. The data suggest that under physiological conditions CO₂ reactivity is related to the basal tone of the cerebrovascular bed. The way in which CO₂ reactivity relates to conductance, therefore, may be a more reliable index of the integrity of the cerebrovascular CO₂ response than the CBF change per se. Analysis of CO₂ reactivity as a function of conductance may facilitate the interpretation of mean and regional CO₂ reactivity and may provide a more meaningful basis for comparison of the CO₂ response between individuals.

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