Brain Injury from Marked Hypoxia in Cats: Role of Hypotension and Hyperglycemia

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SUMMARY The present study identifies several factors that govern brain pathologic response to marked hypoxia. None of 13 cats exposed to 25 minutes of marked hypoxia (FiO₂ = 3.4%; PaO₂ = 17 ± 3 mm Hg, S.D.) that maintained mean arterial blood pressure (MABP) >65 mm Hg were brain injured after reoxygenation and long term survival. In contrast, 12 of 13 exposed to the same hypoxia but that experienced reductions in MABP < 45 mm Hg for 4 ± 1 minutes developed a pattern of brain injury closely resembling that of humans surviving in a persistent vegetative state after cardiorespiratory arrest. Higher serum glucose and lactate concentrations and lower blood pH values significantly correlated with development of hypotension during hypoxia. Four of 8 cats exposed to 21 minutes of marked hypoxia followed by 4 minutes of 100% N₂ breathing that also led to hypotension similarly developed brain injury. Among the hypoxic/hypotensive cats the magnitude of the hyperglycemic response to hypoxia as modulated by 0, 1, or 2 days of preexposure fasting, strongly correlated with occurrence and extent of brain damage. Peak cisterna magna CSF lactate concentrations 10 to 30 minutes into recovery distinguished those animals that remained brain-intact (<13 mM) from those that developed brain damage (>15 mM) with 100% accuracy. Seven cats developed delayed cardiogenic shock 3 to 12 hours into the recovery period. This outcome was predicted by blood pH values <6.70 shortly after resuscitation while all 27 surviving cats exhibited values >6.80.

CARDIOPULMONARY RESUSCITATION saves many lives. However, a proportion of patients subject to cardiac arrest or other forms of major circulatory or respiratory disturbances, following successful resuscitation, survive with severe permanent neurologic deficits and damage to brain.¹ ²

Our laboratory has demonstrated that serum glucose concentration, a previously unsuspected variable, critically determines brain pathologic response to anoxia in conjunction with duration of anoxic exposure.³ ⁴ We have found that, rather than energy depletion, lactic acid accumulation in brain to concentrations >17 to 20 μmol/g correlates with appearance of brain damage.⁵ These previous studies used a circulatory arrest model which had the advantage that no further glucose was conducted to products of metabolism were removed from the brain during exposure. However, anoxic brain damage in humans often results from exposure to hypoxia or an incomplete ischemia rather than to a suddenly developing circulatory stasis. The present study investigates those factors that govern brain pathologic response to marked hypoxia paying a particular attention to the role played by serum glucose concentration.

Material and Methods

a) Animal Preparation

Thirty four adult, quarantined cats of both sexes were used. Eleven were fasted for 2 days, 17 for 1 day, and 6 were fed ad libitum prior to study to vary their hyperglycemic response to hypoxic exposure. On the day of study all cats were anesthetized with IV. pentobarbital, 30 mg/kg, supplemented by additional 10 mg/kg doses as required to suppress the corneal reflex during subsequent procedures. The cats were intubated per os, circumferential ties were placed around the exposed trachea to ensure an airtight fit and the animals were ventilated with room air using a Loosco Respirator (adjusted to yield normal arterial blood gas values).

PE 90 polyethylene catheters were inserted into the right femoral artery and vein through an inguinal cut-down. The cats were infused with 10 ml/kg of 0.9% saline to assure adequate hydration. The arterial catheter was connected to a physiologic pressure transducer (Gould Stratham) to continuously record blood pressure and heart rate on a Brush Gould 480 polygraph. Subcutaneous electrodes inserted over 1) both parietal regions and the frontal air sinus and 2) in the proximal extremities served to record the EEG and ECG.

Arterial blood samples (1.0 ml) were withdrawn twice during the control period; at 5 minute intervals during hypoxia and the first 15 minutes of recovery; and at 10, 20, and finally, 30 minutes intervals thereafter for at least 5 hours. An equal quantity of citrated donor blood was transfused after each blood sample to maintain blood volume. Blood typing and cross-matching was not performed and no adverse reactions occurred since 95% of cats are of the same blood type.⁶ We determined the arterial blood pH, pO₂, and pCO₂ values using a Corning #168 pH/blood gas analyzer from 0.2 ml heparinized blood samples. All values were adjusted for rectal temperature, barometric pressure and hemoglobin content. Rectal temperature was maintained between 38 and 39°C by application of external heat. Additional blood and cisterna magna cerebrospinal fluid (CSF) samples were simultaneously withdrawn. The derived serum and CSF samples were analyzed for glucose and lactate (serum and CSF) and pentobarbital

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concentrations (serum). Glucose concentrations were determined using a Beckman glucose analyzer; lactate using a spectrophotometric method; and blood pentobarbital using a gas-liquid chromatographic method.

b) Exposure

Twenty six cats were exposed to 25 minutes of marked hypoxia by ventilating them with 3.4% O₂ in 96.6% N₂. Eight others were respired with the same gas mixture for 21 minutes (without that they substantially reduced their blood pressure) followed by 4 minutes with 100% N₂ (see below).

c) Recovery

All cats were ventilated with 100% O₂ during resuscitation and for the first 30 minutes thereafter. The oxygen values were then gradually reduced to that of room air always assuring PaO₂ values ≥90 mm Hg. The 15 animals that sustained circulatory collapse were resuscitated with external cardiac massage, 100% O₂ ventilation and epinephrine (0.2 mg) I.V. in cats that remained stable, continuous cardiovascular, blood and CSF compositional, and EEG and ECG monitoring was discontinued 5 hours after exposure. All cats that survived were maintained for 2 weeks with frequent neurologic evaluations. Severely damaged animals required parenteral fluids and handfeeding. Cats that developed seizures were treated with pentobarbital (10 mg/kg, b.i.d.).

d) Termination of Experiment

Seven cats developed a progressive cardiogenic shock after an early good blood pressure response and were killed 3 to 12 hours after they were resuscitated when their MABP had declined to 50 mm Hg. Cats surviving long term were killed after two weeks with a pentobarbital overdose. Their brains were fixed in situ by intravascular saline perfusion followed by buffered 10% formalin, removed and immersion-fixed for an additional 2 weeks. All surfaces and 0.5 cm coronal slices of the brain were then examined grossly. Cresyl violet stained whole-mount histologic sections were prepared from all brain slices. A semiquantitative scale as described in table 1 was used to describe severity and extent of brain damage based on light microscopic examinations.

e) Statistics

All parameters measured were expressed as means ± standard deviations and Student’s t-test was used to define significant differences (p < 0.05) in these parameters among the different exposure and outcome groups. Subgroups were merged when they failed to show significant differences with respect to specific factors analyzed, i.e., cats exposed to hypoxia alone that led to circulatory collapse compared to those additionally respired with N₂; brain-intact animals that maintained compared to those that sustained reductions in blood pressure; brain-injured cats with short and long term survival. When applicable regression curves were fitted, correlation coefficient r was calculated, and corresponding p values obtained.

### Table 1 Distribution of Brain Damage (Selective Neuronal Necrosis) in 34 Cats According to Grade

<table>
<thead>
<tr>
<th>Structure</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>G. cinguli</td>
<td>0</td>
</tr>
<tr>
<td>G. lateralis</td>
<td>1</td>
</tr>
<tr>
<td>G. suprasylvianus</td>
<td>2</td>
</tr>
<tr>
<td>G. ectosylvianus</td>
<td>3</td>
</tr>
<tr>
<td>G. sylvianus</td>
<td>4</td>
</tr>
<tr>
<td>G. rectus</td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td>1</td>
</tr>
<tr>
<td>N. caudatus</td>
<td>2</td>
</tr>
<tr>
<td>Thalamus</td>
<td>3</td>
</tr>
<tr>
<td>Geniculate body</td>
<td>4</td>
</tr>
<tr>
<td>Coll. sup.</td>
<td></td>
</tr>
<tr>
<td>Coll. inf.</td>
<td></td>
</tr>
<tr>
<td>Sub. grisea centr.</td>
<td></td>
</tr>
<tr>
<td>N. pontis</td>
<td></td>
</tr>
<tr>
<td>Purkinje cells</td>
<td></td>
</tr>
<tr>
<td>Inf. olives</td>
<td></td>
</tr>
</tbody>
</table>

- = normal; * = slight; † = moderate; ‡ = marked selective neuronal necrosis.

G. = gyrus, N. = nucleus, Coll. = colliculus, Sub. = substantia.

### Results

#### Brain Pathologic Outcome

Sixteen of 34 cats exposed to 25 minutes of marked hypoxia (8 of which were rendered anoxic by nitrogen breathing for the last 4 minutes) developed brain damage (table 2). All these cats demonstrated a selective neuronal necrosis such as that illustrated in figure 1. The structures damaged are listed in Table 1 which also defines the grading system used to assess severity of brain injury. In no instance were foci of pannecrosis observed. Depending on duration of survival, the affected gray matter structures showed either acute cytologic changes or disappearance of neurons, proliferation of astrocytes and capillaries and infiltration mainly by macrophages. The degrees of severity (slight, moderate, marked) used in table 1 correspond

#### Table 2 Brain Pathologic Outcome of 34 Cats Exposed to Marked Hypoxia with and without Hypertension

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Grade of Brain Injury*</th>
<th>Total Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 min hypoxia N</td>
<td>1 0 0 0 0 13</td>
<td></td>
</tr>
<tr>
<td>(MABP &gt; 65 mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 min hypoxia N</td>
<td>1 0 4 1 7 13</td>
<td></td>
</tr>
<tr>
<td>(MABP &lt; 45 mm Hg for 4±1 min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21 min hypoxia plus 4 min anoxia N</td>
<td>4 1 3 0 0 8</td>
<td></td>
</tr>
<tr>
<td>(MABP &lt; 45 mm Hg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hypoxia was produced by mechanical ventilation with 3.4% O₂; anoxia with 100% N₂.

*Defined in table 1.
to a percentage of affected neurons of <30%, approximately 50% and of >80%, respectively. The distribution and frequency of involvement of affected structures in the 9 brain damaged cats that survived beyond 24 hours is illustrated schematically in figure 2. This histologic type and pattern of distribution of brain injury resembles the anoxic encephalopathy observed in patients surviving in a persistent vegetative state after cardio-respiratory arrest. All 7 cats that developed grade 4 brain injury (table I) also died 3 to 12 hours after resuscitation of delayed cardiogenic shock. Though the surviving animals showed a less extensive damage than did those that were killed early because of cardiogenic shock, the distribution and type of damage were similar. All 13 cats that maintained their blood pressure (MABP > 65 mm Hg) and 5 that sustained a circulatory collapse remained brain intact.

**Arterial Blood Oxygen Tension Correlations**

Animals respired with 3.4% O₂ for 21 (N = 8) or 25 (N = 26) minutes reduced their average PaO₂ values from 106 ± 2 to 17 ± 3 mm Hg (mean ± S.D., N = 144 samples). Animals respired with 100% N₂ following 21 minutes of hypoxia further reduced their PaO₂ values to 2 mm Hg. During hypoxia, the individual animals and the animals of the different outcome groups showed little variation of their PaO₂ values. The 16 cats that later exhibited brain injury experienced slightly higher mean ± S.D. PaO₂ values (18 ± 2 mm Hg) during hypoxia than did the 18 cats that remained brain intact (17 ± 2 mm Hg). The 7 cats that developed cardiogenic shock several hours after they were resuscitated exhibited lower mean ± S.D. PaO₂ values (124 ± 64 mm Hg) during the first 30 minutes after reoxygenation with 100% O₂ than did the 27 animals that survived long term (310 ± 177 mm Hg) (p < 0.001).

**Arterial Blood Pressure Correlations**

Only those exposures to hypoxia culminating in a mean ± S.D. of 4 ± 1.5 minutes of circulatory collapse (MABP < 45 mm Hg) showed a potential for causing brain damage (table 2). We induced late developing circulatory collapse in 8 additional cats respired with 3.4% O₂ for 21 minutes (during which they maintained their MABP) by respiring them with 100% N₂ for a final 4 minutes (table 2). Only the latter circumstance produced cats that experienced a less marked hyperglycemia during hypoxia/hypotension (see below).

The lowest MABP in the hypoxia/hypotension group expressed as mean ± S.D. was 27 ± 13, 22 ± 16, and 7 ± 6 mm Hg in the cats that survived brain intact (N = 5), that survived brain injured (N = 9) and that developed brain damage but succumbed of delayed cardiogenic shock (N = 7), respectively. All cats restored their MABP to control values (125 mm Hg) within 5 minutes of reoxygenation. The 27 cats that recovered maintained stable blood pressures while the 7 that developed cardiogenic shock showed progressive blood pressure reductions beginning after 1½ to several hours.
Glucose Correlations

The extent of hyperglycemic response to hypoxia was modulated by duration of prior food deprivation. Six cats fed the day of procedure showed peak serum glucose concentration means ± S.D. of 759 ± 97 while 17 1-day food-deprived and 11 2-day food-deprived animals showed peak values of 494 ± 164 and 240 ± 82 mg/dl, respectively. The level of serum glucose concentration, in turn, strongly affected both whether the animals were to develop circulatory collapse during hypoxia and, in such animals, whether and the extent to which they would suffer brain injury (fig. 3). The 13 cats that maintained MABP >65 mm Hg experienced peak serum glucose concentrations of 377 ± 184 compared to the 13 with MABP <45 mm Hg that experienced concentrations of 566 ± 251 mg/dl, S.D. (p < 0.02). The hypoxic MABPs plotted against corresponding serum glucose concentrations show a significant inverse linear correlation (table 3).

The cisterna magna CSF glucose concentrations paralleled those in serum but remained at lower levels and showed a considerable lag with maximal values attained about 1 hour later than in serum. Concomitant with reductions in MABP < 45 mm Hg the CSF glucose concentrations sharply declined by approximately 50 mg/dl. Brain damaged cats experienced significantly higher blood and CSF glucose concentrations both during and following exposure than did brain intact animals.

Lactic Acid Correlations

All cats progressively accumulated lactate in serum and CSF during hypoxia. Cats that survived with or without brain injury increased plasma lactate to an average of 12 mM during hypoxia and restored these values to control levels (1.2 mM) by 90 minutes into recovery. In contrast, brain injured cats that developed delayed cardiogenic shock augmented their mean serum lactate concentrations to significantly higher values (17 mM) during hypoxia and continued to maintain elevated levels until euthanized because of declining blood pressure. Serum lactate during hypoxia correlated with serum glucose and (inversely) with MABP (table 3).

Lactic acid correlations showed similar elevations in cistern magna CSF lactate concentrations during hypoxia (fig. 4). However, the brain injured cats showed much higher CSF lactate concentrations during the first 90 minutes of recovery than did the brain intact (p < 0.001). The 6 brain damaged cats attained peak CSF lactate concentrations >15 mM (mean ± S.D. = 17.5 ± 1.3 mM) while none of 8 intact cats achieved values >13 mM (10.1 ± 2.2 mM) (p < 0.001). Significant linear correlations were found between peak CSF lactate (10 to 30 minutes into recovery) and lowest MABP measurements, and peak CSF lactate and highest serum glucose concentrations during hypoxia (r = 0.82 and 0.94, respectively).

Arterial Blood PCO₂

All groups showed similar changes in mean PaCO₂ values during the control and exposure periods. During hypoxia with ventilator settings unchanged the cats experienced reductions in PaCO₂ values from 32 to 15 mm Hg. The group with grade 4 brain damage and delayed cardiogenic shock experienced a mean PaCO₂ value of 80 mm Hg during the first hour postexposure which declined to 40 to 50 mm Hg during the remainder of the experiment.
der of survival. The brain injured cats that survived experienced a transient mean PaCO₂ value of 45 mm Hg during the first 15 minutes of recovery while those that remained brain intact maintained near normal values throughout recovery.

**Arterial Blood pH**

Following an initial increase in blood pH, all groups experienced gradual reductions which reached their nadirs 5 to 10 minutes into recovery. The brain intact cats experienced average lowest pH values of 7.05, the surviving brain damaged ones of 6.95, and the cats developing diffuse brain damage and, concomitantly, cardiogenic shock of 6.65. The lowest blood pH during hypoxia reliably predicted animal survival or death from delayed cardiogenic shock (p < 0.001) but did not differentiate brain outcome in survivors. Arterial blood pH during hypoxia also correlated significantly with blood pressure (table 3).

**Heart Rate, Hematocrit, and Pentobarbital**

The cats of the several outcome groups showed similar heart rate and hematocrit values during the control period, hypoxia, and recovery. During hypoxia the hematocrit increased from a mean of 32 to 42% and stabilized near 35% by 20 minutes into recovery. At the onset of hypoxia, all animal groups showed similar average serum pentobarbital concentrations (26 ± 8 microgm/ml).

**EEG**

The EEG showed no changes in amplitude or frequency during hypoxia unless MABP declined below 45 mm Hg. All 21 cats that experienced such marked MABP reductions, whether induced by hypoxia or nitrogen breathing, markedly reduced their EEG amplitudes and frequencies. However, these alterations failed to correlate with brain pathologic outcome. Also, EEG recovery during the first 3 hours after exposure was similar between the outcome groups. Therefore, the EEGs of intact cats approached control values while those of the brain injured groups showed continued depression most marked in the delayed cardiogenic shock group.

**Neurologic Outcome**

The brain-intact cats showed no neurologic abnormalities after recovery from anesthesia. Since the 4 brains of the injured cats all died from delayed cardiogenic shock within 12 hours while still anesthetized, neurologic assessment was not possible. The 1 brain of the delayed brain damaged cats that survived 1 to 16 days all showed neurologic impairments throughout survival which included generalized muscular hypertonus and inability to stand, walk or feed during the first 3 to 5 days. Eight of 9 developed seizures. A single cat remained comatose (death at 24 hours) while the remainder were responsive from 12 hours onward. These injured cats showed intermittent, generalized tonic-clonic convulsions starting 19 to 72 hours after exposure and continuing for about 24 hours or until they died. During such seizures, the EEGs typically showed 3/second spike and wave patterns. Though the neurologic deficits decreased with prolonged survival, most animals continued to require hand feeding.

**Discussion**

The present study emphasizes two variables that importantly define brain pathologic response to severe hypoxia (PaO₂ = 17 mm Hg) lasting up to 25 minutes. 1) The hypoxia must lead to marked reductions in blood pressure to cause brain injury. 2) When marked hypoxia was associated with fall in blood pressure, extent of brain damage was determined by serum glucose concentration. Exposure to hypoxia without fall in blood pressure did not injure the brain agreeing with the finding that humans also can tolerate marked hypoxia without brain injury. 10, 11

Serum glucose concentration at the time of exposure to anoxia or ischemia in conjunction with exposure duration critically determines both occurrence of brain injury and its distribution. 3, 4, 12-14 The present study demonstrates these same influences also operate with respect to exposure to hypoxia/hypotension. The cat is especially suited to investigate such influences because its hyperglycemic response to hypoxia can be modified through a wide range (from 70 to 910 mg/dl) simply by varying duration of food deprivation prior to exposure.

Anesthetized animals that are slightly hypoglycemic from food deprivation require more than 10 minutes of anoxia to damage their brain. 4 Thus, our cats with serum glucose concentrations less than 250 mg/dl that experienced hypoxia/hypotensive episodes lasting about 4 minutes generally did not sustain brain damage while those with higher values did.

That humans show similar relations between levels of serum glucose concentration and brain pathologic response to anoxia is suggested by the finding that patients comatose after cardiac arrest who later awaken and recover full brain function are mainly those with serum glucose concentrations below 300 mg/dl while those who develop permanent, severe deficits are largely those with more marked hyperglycemia. 15 However, humans often experience stress of one type or another (including hypoxia) prior to experiencing anoxia which stimulates a catecholamine response, hepatic glycogenolysis, and hyperglycemia. Humans also often experience increased serum glucose concentrations as a consequence of intravenous glucose infusions in the hospital setting. This may explain why humans commonly exhibit hemispheric patterns of damage from brief anoxia similar to that produced in the present study. 2, 16

Cerebral blood flow becomes pressure passive when hemoglobin saturation with oxygen falls below 60%. 17 The operation of this mechanism would have markedly reduced cerebral blood flow during marked hypotension or circulatory collapse as occurred in 15 cats in the present study. The addition of cerebral ischemia and of marked hypoxemia likely then led to a brain tissue anoxia and brain damage. 18 The presently defined
sharp dichotomy in brain pathologic response to hypoxia as compared to anoxia is understandable from their striking differences in induced brain metabolic changes. Lactic acid accumulation in brain above a threshold concentration of 17 to 20 \(\mu\)mol/g, as occurs under anoxic circumstances, strongly correlates with irreversible brain damage while lactic acid accumulation to concentrations below this level are associated with functional recovery and no brain injury.\(^\text{4, 5, 19}\)

Monkeys exposed to a hypoxia of similar magnitude and duration as in the present study, show brain tissue lactic acid concentrations that reach a constant level substantially below the threshold required to injure provided their blood pressure was well maintained.\(^\text{20}\)

However, when their blood pressure declined below certain limits, a sustained stimulation of glycolysis developed and brain tissue lactic acid concentrations increased rapidly to values above threshold for injury.\(^\text{20}\) Only with such a sustained stimulation of glycolysis brought about by anoxia does glucose availability define magnitude of lactic acid accumulation in brain.

The above interpretations are reflected in our study:

1. A wide range of hyperglycemia failed to influence CSF lactic acid accumulation and brain pathologic outcome during hypoxia with maintained blood pressure;
2. Serum glucose concentration significantly affected outcome only when the marked hypoxia was combined with a marked fall in blood pressure;
3. During critical reductions in blood pressure the CSF glucose concentrations fell precipitously and lactate concentrations began steep increases.

The close correlation between cisterna magna CSF lactate concentrations and pathologic outcome supports the view that lactic acid accumulation in brain plays a critical role in damaging brain. The peak CSF-lactate concentrations distinguished brain damaged from brain intact animals with 100% reliability and before any other parameter, even though lactate is thought to diffuse slowly from the intracellular- to the extracellular compartments and even though changes in cisterna magna CSF reflect distantly alterations that take place in the cerebral hemispheres.\(^\text{21, 22}\)

While cisterna magna CSF lactate concentrations delineated brain pathologic outcome early and accurately that of serum failed to do so supporting Posner and Plum's\(^\text{23}\) observation that changes in blood and CSF lactic acid concentrations commonly vary independently.

References

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