

# The Effects of Dextrose Infusion and Head Position on Neurologic Outcome after Complete Cerebral Ischemia in Primates: Examination of a Model

William L. Lanier, M.D.,\* Kenneth J. Stangland, M.D.,† Bernd W. Scheithauer, M.D.,‡  
James H. Milde,§ John D. Michenfelder, M.D.¶

The hypothesis that iv dextrose infusion prior to—and head position during—cerebral ischemia would influence the severity and pattern of neurologic injury was tested in primates. Fifteen pigtail monkeys weighing  $3.3 \pm 0.2$  kg (mean  $\pm$  SE) were subjected to 17 min complete cerebral ischemia followed by 24 h intensive care treatment and neurologic assessment for an additional 72 h. Monkeys were given 50 ml iv infusions of either dextrose 5% in 0.45% saline solution ( $n = 8$ ) or lactated Ringer's solution ( $n = 7$ ) during the preparatory period. This volume corresponds to approximately 1 l/70 kg individual. These same monkeys were placed in either the lateral ( $n = 3$ ), prone ( $n = 5$ ), or supine ( $n = 7$ ) position during the ischemic period. Two monkeys failed to meet preestablished protocol criteria and were excluded from data analysis. Blood glucose immediately preischemia in the dextrose-treated group ( $181 \pm 19$  mg  $\cdot$  dl<sup>-1</sup>) was not significantly greater than in the group given lactated Ringer's solution ( $140 \pm 6$  mg  $\cdot$  dl<sup>-1</sup>;  $P = 0.07$ ). Dextrose infusion resulted in significantly greater cerebral injury at 96 h postischemia when comparing both neurologic ( $P < 0.05$ ) and histopathology ( $P < 0.05$ ) scores. Specifically, dextrose administration resulted in the greatest injury to the insular cortex, thalamus, Purkinje cells, and substantia nigra. Although blood glucose was  $<250$  mg  $\cdot$  dl<sup>-1</sup> in all monkeys at the time of complete cerebral ischemia, there was a high correlation between blood glucose rank and neurologic function rank ( $r_s = 0.76$ ;  $P < 0.005$ ). The authors were unable to note any effect of head position on the distribution of histopathologic lesions. Prior to removing the brain for histopathologic studies, four monkeys were given repeat infusions of 50 ml dextrose 5% in 0.45% saline solution over  $11 \pm 1$  min. These infusions produced increases in blood glucose from  $56.7 \pm 7.6$  to  $244 \pm 24.9$  mg  $\cdot$  dl<sup>-1</sup> ( $P < 0.01$ ) and increases in brain glucose from  $1.64 \pm 0.22$  to  $5.11 \pm 0.48$   $\mu$ mol  $\cdot$  g<sup>-1</sup> ( $P < 0.01$ ). (Key words: Brain: ischemia; metabolism; resuscitation. Heart: cardiac arrest. Metabolism: glucose. Toxicity: glucose.)

A PREVIOUS REPORT from our laboratory noted that monkeys given iv dextrose infusions and subsequently exposed to complete cerebral ischemia in the supine position sustained the greatest injury to portions of the brain sup-

plied by the posterior circulation.<sup>1</sup> We also noted that the two monkeys with the highest preischemic blood glucose values (219 and 231 mg  $\cdot$  dl<sup>-1</sup>) exhibited the worst neurologic outcome of the 21 monkeys studied (unpublished data). Although we could not demonstrate that sugar administration prior to—or head position during—the period of complete cerebral ischemia affected the outcome of that study, sugar administration and head position are thought possibly to affect the model.

There is a large body of data that suggests that elevated blood glucose or a history of sugar administration will augment postischemic cerebral injury in laboratory animals<sup>2-6,\*†‡</sup> and humans.<sup>6-9</sup> However, many of these laboratory reports used sugar loads that exceed clinical doses. That small differences in blood glucose values may influence postischemic neurologic outcome in laboratory studies has been retrospectively suggested by Todd *et al.*<sup>††</sup>

Blood or blood components remaining in the cerebral vasculature at the time of cerebral ischemia may also augment postischemic cerebral damage.<sup>10-15,‡‡</sup> Ames<sup>‡‡</sup> and Fisher<sup>14</sup> have hypothesized that blood pooling in dependent cerebral areas during periods of ischemia may affect the distribution of postischemic neurologic injury. Thus, our previous finding of increased posterior cerebral injury in supine monkeys exposed to complete cerebral ischemia may be due in part to the head position during the ischemic period.<sup>1</sup>

The current study was designed to test the hypothesis that clinically relevant doses of iv dextrose prior to—and head position during—complete cerebral ischemia would affect the severity and pattern of neurologic injury in monkeys exposed to 17 min of complete cerebral ischemia.

## Methods

### STUDY SUBJECTS AND PREISCHEMIC PREPARATION

Fifteen unmedicated pigtail monkeys (*Macaca nemestrina*) ages 14–42 months of either sex, weighing  $3.3 \pm 0.2$

\* Senior Associate Consultant in Anesthesiology, Mayo Clinic; Assistant Professor of Anesthesiology, Mayo Medical School.

† Fellow in Anesthesiology, Mayo Clinic.

‡ Consultant in Surgical Pathology, Mayo Clinic; Associate Professor of Surgical Pathology, Mayo Medical School.

§ Research Associate, Mayo Clinic.

¶ Consultant in Anesthesiology, Mayo Clinic; Professor of Anesthesiology, Mayo Medical School.

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Address reprint requests to Dr. Lanier: Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55905.

\*\* Myers RE: Anoxic brain pathology and blood glucose (abstract). *Neurology* 26:345, 1976.

†† Todd MM, Chadwick HS, Shapiro HM, Goodman RM: Outcome after cardiac arrest: The role of plasma glucose (abstract). *ANESTHESIOLOGY* 55:A265, 1981.

‡‡ Ames A: Discussion. *Arch Neurol* 29:364–366, 1973.

kg (mean  $\pm$  SE), were studied. The monkeys were uniformly fed but received only water *ad lib* the last 24 h before the experiment. Monkeys were initially anesthetized with halothane 0.5% and nitrous oxide 66% in oxygen. Pancuronium 2 mg and glycopyrrolate 0.05 mg were given *im* to facilitate tracheal intubation with a cuffed wire-spiral reinforced tube, and ventilation was controlled with a Harvard® pump.

Catheters were placed in the abdominal aorta *via* the femoral artery for blood sampling and pressure monitoring and in a peripheral vein for fluid and drug infusions. Additional doses of pancuronium 0.02 mg  $\cdot$  kg<sup>-1</sup> *iv* were given as needed. A two-channel EEG was recorded using bifrontal and biparietal needle electrodes. Body temperature was measured with a rectal thermistor and maintained near 37° C throughout the experiment using heating pads and heat lamps when needed. End-tidal CO<sub>2</sub> was monitored with a mass spectrometer (Perkin-Elmer, Model 1100), and arterial blood gases were determined by electrodes (Instrumentation Laboratory, Inc., Lexington, MA) at 37° C. Arterial blood gases were measured immediately preischemia and frequently postischemia. Serum Na<sup>+</sup> and K<sup>+</sup> were determined preischemia, and blood glucose was determined using indicator-impregnated strips (Chemstrip bG®, Biodynamics, Indianapolis, IN). The latter permitted the rapid identification of blood glucose levels at 20–30 mg  $\cdot$  dl<sup>-1</sup> increments over a range of 20–240 mg  $\cdot$  dl<sup>-1</sup>, and these values are reported to correlate well with values obtained from a Beckman® Glucose Analyzer ( $r = 0.978$ ;  $P < 0.0001$ ).§§¶¶

#### RANDOMIZATION

Monkeys were divided into groups according to position and fluid infusion. Group D monkeys ( $n = 8$ ) received dextrose 5% in 0.45% saline solution 50 ml *iv*, and Group R monkeys ( $n = 7$ ) received lactated Ringer's solution 50 ml *iv* during the preparatory period. This volume of fluid, corresponding to approximately 1 l/70 kg individual, was infused over a 10–15 min period approximately 30 min before induction of ischemia. The monkeys were further subdivided randomly into Group S ( $n = 7$ ), who were placed in the supine position during ischemia, Group L ( $n = 3$ ) in the left lateral decubitus position, and Group P ( $n = 5$ ) in the prone position.

#### PRODUCTION OF ISCHEMIA

Complete cerebral ischemia was produced by a method previously described by Bleyaert *et al.*<sup>16</sup> and Gisvold *et*

*al.*<sup>17</sup> using modifications described by Steen *et al.*<sup>1</sup> Halothane was discontinued for 3 min, and anesthesia was maintained with nitrous oxide 66% in oxygen. Rapid induction of hypotension (within 1 min) was induced by administration of trimethaphan 20–40 mg *iv* until a mean arterial pressure (MAP) of approximately 50 mmHg was achieved. At this point, a collapsible neck tourniquet was inflated to 1,500 mmHg for 17 min, and the monkeys were ventilated with 100% O<sub>2</sub> during the period of cerebral ischemia. A tendency to hypertension during the first 5 min of ischemia was treated with additional administration of trimethaphan and the addition of positive end-expiratory airway pressure (PEEP) to maintain MAP at 40–80 mmHg during the ischemic period. After 14 min of ischemia, a norepinephrine (NE) infusion was started at 0.4  $\mu$ g  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup> and adjusted as needed to maintain MAP at 80 mmHg before neck tourniquet deflation. Immediately after tourniquet deflation, MAP always abruptly decreased. Further adjustments of the NE infusion were made to increase MAP to 80–110 mmHg during the immediate postischemic period.

Completeness of cerebral ischemia was monitored using <sup>133</sup>Xe, as previously described by Steen *et al.*<sup>1</sup>

#### POSTISCHEMIC TREATMENT

Optimal life support was provided for 24 h postischemia with a minimum of one technician and one physician in attendance.

Paralysis and controlled ventilation were maintained until continuous EEG activity had returned for 1 h. Monkeys received 100% inspired O<sub>2</sub> for the first 2 h after ischemia followed by N<sub>2</sub>O 50% in O<sub>2</sub> thereafter until extubation. The latter provided analgesia and sedation during immobilization in an attempt to avoid a previously reported severe hypertensive reaction.<sup>1,\*\*\*</sup> PaCO<sub>2</sub> was maintained at 25–30 mmHg and PaO<sub>2</sub> was maintained above 100 mmHg by increasing fractional inspired O<sub>2</sub> concentration (FI<sub>O<sub>2</sub></sub>) as needed. A minimum of 2–3 cm PEEP was used. Respiratory care included tracheal suctioning as needed, intermittent deep-lung inflations (sighing), chest physiotherapy, and turning the monkeys from side to side every 4 h.

At 1 h after return of continuous EEG activity (approximately 2.5 h postischemia), pancuronium-induced neuromuscular blockade was reversed with neostigmine 0.07 mg  $\cdot$  kg<sup>-1</sup> *iv* and glycopyrrolate 0.012 mg  $\cdot$  kg<sup>-1</sup> *iv*. The monkeys were weaned from the ventilator and extubated if spontaneous ventilation was deemed adequate

§§ Package insert: Chemstrip bG. Indianapolis, Boehringer Mannheim Diagnostics, Inc.

¶¶ Piepho SL, Kloefer HG, Suther C: Evaluation of three systems for measuring blood glucose (abstract). *Diabetes* 29:34A, 1980.

\*\*\* Bleyaert AL, Safar P, Stezoski SW, Nemoto EM, Moossy J: Amelioration of postischemic brain damage in the monkey by immobilization and controlled ventilation (abstract). *Crit Care Med* 6:112–113, 1978.

as judged by the presence of carinal and pharyngeal reflexes, maintenance of a  $\text{PaCO}_2 < 35$  mmHg, and the presence of hemodynamic stability. At the time of extubation, the femoral artery catheter was removed; and, thereafter, femoral artery samples for blood gases were obtained by percutaneous needle puncture as needed to evaluate unexplained tachypnea, tachycardia, cardiac dysrhythmias, lethargy, or discoloration of the mucous membranes.

MAP was maintained at 80–120 mmHg during the immediate postischemic period until the time of femoral artery decanulation. An infusion of NE was often needed in the immediate postischemic period. Later, trimethaphan ( $3\text{--}15 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) was used as needed in two animals (Groups D and S and Groups R and S) to treat hypertension. Dextrose 5% in 0.45% saline solution was infused at  $4 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  during the first 24 h. If further fluid replacement was deemed necessary, additional iv infusions of lactated Ringer's solution  $5\text{--}10 \text{ ml} \cdot \text{kg}^{-1}$  were given. Thereafter, monkeys were further hydrated as during the first 24 h, were intermittently hydrated with  $10\text{--}20 \text{ ml} \cdot \text{kg}^{-1}$  lactated Ringer's solution subcutaneously, or were given fluids per os as determined by their activity. Fluid requirements after the first 24 h were determined by physical examination. Potassium chloride was added to iv fluids as needed as determined by measuring serum  $\text{K}^+$ . Gentamicin  $1 \text{ mg} \cdot \text{kg}^{-1}$  iv was given every 8 h during the first 2 days. Benzathine penicillin 300,000 units and procaine penicillin 300,000 units im were given daily.

When their conditions permitted, monkeys were moved to padded open pens, and when they were judged to be near normal, they were returned to their cages. In all animals, ages were determined from birth records.

#### EXCLUSIONS

Animals that did not meet all preestablished protocol criteria were excluded from data analysis before the final 96-h evaluation. The decision to exclude animals was made by a blinded observer (J.D.M.), who was unaware of treatment groups. Exclusion was based on strict criteria: a preischemic blood glucose  $> 250 \text{ mg} \cdot \text{dl}^{-1}$ ; evidence of incomplete ischemia; severe cardiopulmonary complications, such as pulmonary edema, resulting in a postischemic  $\text{PaO}_2 < 60$  mmHg and/or a  $\text{PaCO}_2 > 45$  mmHg; failure to achieve a postischemic MAP of  $> 80$  mmHg within 3 min after cuff deflation; and thereafter, a MAP  $< 70$  mmHg for  $> 60$  min or of  $< 50$  mmHg at any point or a MAP  $> 130$  mm for more than 1 h.

Because Pulsinelli *et al.* have shown that histologic changes after a period of cerebral ischemia require more than 24 h to mature,<sup>18</sup> we decided prior to the study onset to exclude monkeys from data analysis who died before 48 h postischemia. This restriction was not felt to affect outcome because Steen *et al.*,<sup>1</sup> whose monkeys were con-

tinuously observed for 96 h, had no monkeys die within the first 48 h postischemia without first violating age, glucose, or cardiopulmonary exclusion criteria.

#### NEUROLOGIC FUNCTION POSTISCHEMIA

Neurologic function was evaluated at 26, 48, 72, and 96 h postischemia by the same blinded observer (J.D.M.). A previously described neurologic examination and scoring system were used.<sup>1</sup> Briefly, this system scored monkeys according to their level of consciousness, respiration, cranial nerve function, motor and sensory function, and behavior. The results were expressed as per cent neurologic function, where 100% was normal and 0% was apparent brain death.

#### HISTOPATHOLOGIC AND CEREBRAL GLUCOSE EVALUATION

After the final clinical evaluation, the 13 surviving monkeys were reanesthetized with ketamine  $3\text{--}5 \text{ mg} \cdot \text{kg}^{-1}$  im and paralyzed with pancuronium 1 mg iv. The trachea was intubated, and ventilation was controlled. Anesthesia was maintained with halothane 0.5% in 50%  $\text{N}_2\text{O}$  and  $\text{O}_2$ . A craniotomy was performed in four monkeys, and the dura overlying the frontal lobes was excised. Rectal temperature and end-tidal  $\text{P}_{\text{CO}_2}$  were maintained near  $37^\circ \text{C}$  and 32 mmHg, respectively. In these four monkeys, 50 ml of dextrose 5% in 0.45% saline solution was infused over  $11 \pm 1$  min. Cerebral biopsies were taken immediately before infusion and 3 min after infusion completion, using a punch biopsy system that deposits brain tissue into liquid nitrogen within 1 s. Each sample was analyzed using the enzymatic fluorometric technique described by Lowry *et al.*<sup>19</sup> for glucose. Blood glucose was measured with each brain biopsy and, additionally, when one-half of the 50 ml dextrose solution had been infused, using an enzymatic spectrophotometric technique.<sup>20</sup> In all 13 surviving monkeys, a left thoracotomy was performed, and they were killed by infusing 500 ml of 4% buffered paraformaldehyde into the left ventricle at a pressure of 100 mmHg while the descending thoracic aorta was cross-clamped and the right atrium was opened.<sup>16</sup> One hour later, the brains were removed, weighed, and placed in buffered paraformaldehyde. All brains were fixed for 4 weeks prior to gross and microscopic examinations by a neuropathologist (B.W.S.), who was blinded as to treatment groups and neurologic outcome. Coronal whole-mount, paraffin-embedded microsections were cut at  $6 \mu$  thicknesses and were stained by the hematoxylin-and-eosin method. Representative sections of cerebral cortex, basal ganglia, thalamus, midbrain, pons, medulla, and cerebellum were graded according to the type and extent of histopathology, as previously described.<sup>1,16,17</sup>

Total histopathology scores and regional histopathol-

TABLE 1. Control Physiologic Variables

	Monkey Group				
	D (n = 7)	R (n = 6)	L (n = 2)	P (n = 5)	S (n = 6)
Weight (kg)	3.3 ± 0.2	3.3 ± 0.5	3.2 ± 0.1	3.2 ± 0.5	3.4 ± 0.4
Pa <sub>O<sub>2</sub></sub> (mmHg)	159 ± 7	166 ± 13	176 ± 11	163 ± 14	157 ± 9
Pa <sub>CO<sub>2</sub></sub> (mmHg)	32 ± 1	32 ± 1	33 ± 0	33 ± 1	31 ± 0
pH	7.45 ± 0.02	7.46 ± 0.02	7.49 ± 0.01	7.45 ± 0.02	7.45 ± 0.01
Buffer base (mEq · l <sup>-1</sup> )	45 ± 1	45 ± 1	48 ± 1	45 ± 1	44 ± 0
Hct %	34 ± 1	35 ± 2	34 ± 0	36 ± 1	32 ± 1
MAP (mmHg)	70 ± 5	62 ± 5	75 ± 5	65 ± 6	64 ± 5
Heart rate (beats · min <sup>-1</sup> )	153 ± 3	147 ± 9	160 ± 0	142 ± 7	155 ± 7
Temperature (° C)	36.9 ± 0.1	37.2 ± 0.1	36.7 ± 0.1	37.0 ± 0.1	37.1 ± 0.1
Blood glucose (mg · dl <sup>-1</sup> )	181 ± 19	140 ± 6	180 ± 0	158 ± 23	160 ± 18
Serum Na <sup>+</sup> (mEq · l <sup>-1</sup> )	144 ± 2	150 ± 2	146 ± 2	147 ± 2	148 ± 3
Serum K <sup>+</sup> (mEq · l <sup>-1</sup> )	4.0 ± 0.1	4.0 ± 0.2	4.0 ± 0.2	4.0 ± 0.2	4.1 ± 0.1

All values are expressed as mean ± SE.

There were no statistically significant differences between groups. Group L monkeys were not included in statistical comparisons by po-

sition due to the small number of subjects.

MAP = mean arterial pressure.

ogy scores were compared within and among the various groups. To evaluate the latter, the brain was divided into left and right by hemispheres. Anterior and posterior scores were divided according to brain structures supplied by the anterior and posterior circulations, as determined by our pathologist (B.W.S.). Due to a disparate number of areas compared in anterior and posterior regions, raw histopathology scores were corrected according to the possible number of histopathology points in either area.

#### RADIOGRAPHIC STUDIES

Radiographic studies were performed in one additional monkey to determine if contrast material would pool in dependent brain areas in the absence of blood flow. The monkey was anesthetized with pentobarbital 65 mg iv. Pancuronium 1 mg iv was given to facilitate tracheal intubation, and ventilation was controlled. An angiographic catheter was introduced into the thoracic aorta *via* a femoral artery approach. A tourniquet was placed around the neck as in monkeys used for neurologic function studies. With the animal in the supine position, 30 ml of Vascoray® 76% (Mallinckrodt, Inc., St. Louis, MO) was injected into the aortic arch over 4 s, followed immediately by inflation of the neck tourniquet to 1,500 mmHg. Posterior-anterior and lateral cerebral angiograms were performed with the animal sequentially placed in the supine, prone, left lateral decubitus, and right lateral decubitus positions. Fifteen minutes were allowed between position changes and angiography to allow equilibration of contrast pooling.

#### STATISTICAL EVALUATION

The statistical significance of postischemic differences in neurologic function, histopathologic scores, and blood

glucose values between the various groups was evaluated by the two-tailed Mann-Whitney rank sum test. Comparison of physiologic variables other than blood glucose were evaluated by unpaired *t* tests. The two Group-L monkeys were not included in comparisons of statistical significance according to position due to the small number of subjects. Correlation between neurologic function ranks, histopathology ranks, and blood glucose ranks were assessed using the Spearman rank correlation coefficient. A probability of less than 0.05 was considered significant. All mean values are reported with the standard error of the mean.

#### Results

Thirteen monkeys fulfilled all protocol criteria and were included in the final analysis. Division of groups according to iv fluid history and position during ischemia is noted in table 1.

#### EXCLUSIONS

Two monkeys were excluded from the study prior to the 96-h evaluation. One monkey (Groups D and L) had a blood glucose of 400 mg · dl<sup>-1</sup> immediately before initiation of cerebral ischemia. Life support was terminated 5 h postischemia, at which time EEG activity had not continuously returned. A second monkey (Groups R and S) died of a respiratory arrest 20 h postischemia and prior to the 24 h neurologic evaluation. The brain was grossly normal at necropsy, and the origin of the respiratory arrest was not determined.

#### PHYSIOLOGIC VARIABLES

Control physiologic variables are listed in table 1.

There were no statistically significant differences in physiologic variables between Groups D and R at any

TABLE 2. Time to Onset of EEG Parameters

EEG Parameter	Monkey Group				
	D (n = 7)	R (n = 6)	L (n = 2)	P (n = 5)	S (n = 6)
Isoelectric onset (s)	18 ± 2	19 ± 2	24 ± 6	20 ± 2	16 ± 1*
Burst suppression return (min)	35 ± 3	33 ± 2	34 ± 4	36 ± 2	33 ± 4
Continuous return anterior (min)	100 ± 28	59 ± 8	125 ± 91	65 ± 7	79 ± 24
Continuous return posterior (min)	103 ± 27	69 ± 10	125 ± 91	80 ± 6	81 ± 24

The two Group L monkeys were not included in statistical comparisons by position due to the small number of subjects.

\* Significant difference between Group P and Group S ( $P < 0.05$ )

measurement period. Specifically, the difference between blood glucose in Group D ( $181 \pm 19 \text{ mg} \cdot \text{dl}^{-1}$ ) and that in Group R ( $140 \pm 6 \text{ mg} \cdot \text{dl}^{-1}$ ) achieved significance only at a  $P$  level of 0.07 (Mann-Whitney rank sum test).

COMPLETENESS OF ISCHEMIA

Cerebral ischemia was complete in all monkeys. No  $^{133}\text{Xe}$  was detected in the brain during ischemia.

EEG DATA

EEG data are summarized in table 2. The time between neck tourniquet inflation and onset of an isoelectric EEG was significantly longer in Group P ( $20 \pm 2 \text{ s}$ ) than Group S ( $16 \pm 1 \text{ s}$ ;  $P < 0.05$ ). There were no significant differences among groups in the time of EEG return after neck tourniquet deflation (table 2).

SEIZURE ACTIVITY POSTISCHEMIA

Seizure activity on the EEG or by clinical exam was never noted during the study.

TIME TO EXTUBATION

Duration of postischemic tracheal intubation was significantly greater in Group D ( $307 \pm 30 \text{ min}$ ) than in Group R ( $192 \pm 7 \text{ min}$ ;  $P < 0.01$ ). Clinical evidence of pulmonary edema was not noted in any animal. After the initial extubation, two monkeys (both in Groups P and R) required reintubation, although these data were not included in the earlier calculations. One of these monkeys had the best neurologic and histopathologic outcome of any monkey studied, while the other monkey had an intermediate neurologic outcome.

NEUROLOGIC OUTCOME

Dextrose-infused monkeys had a significantly worse neurologic outcome at 96 h postischemia than lactated Ringer's solution-treated monkeys (fig. 1). The mean neurologic function score was  $79 \pm 5\%$  in Group D and

$98 \pm 2\%$  in Group R. Differences achieved a  $P < 0.05$  by Mann-Whitney rank sum test. Four of six Group R monkeys had no detectable neurologic deficits at 96 h postischemia. No Group D monkey had complete return of neurologic function. There was a highly significant correlation between preischemic blood glucose rank and neurologic function rank, regardless of the iv fluids given during the preparatory period ( $r_s = 0.76$ ;  $P < 0.005$ ) (fig. 2). Three of seven Group D monkeys were blind, while no Group R monkey was blind. Ataxia occurred in all seven Group D monkeys but in only one Group R monkey. The difference in ataxia scores achieved a  $P < 0.02$  by rank sum test. Head position at the time of ischemia had no effect on neurologic outcome (fig. 1). Lateralizing neurologic deficits were not seen in the two Group L

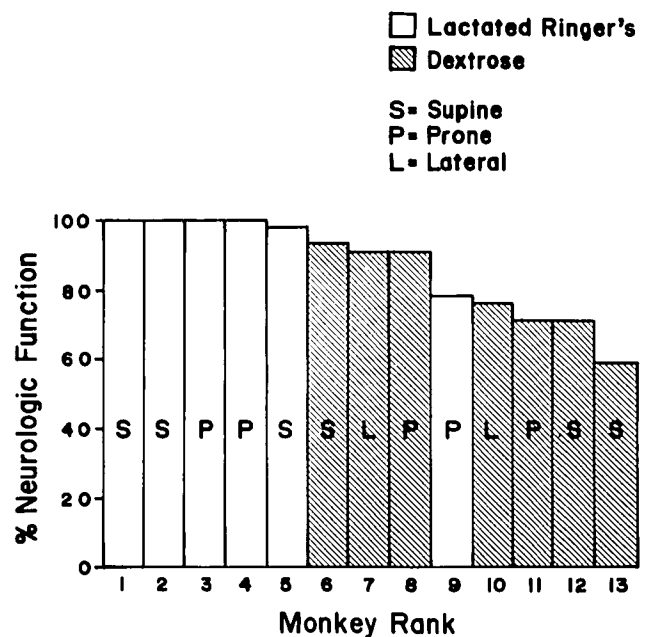


FIG. 1. Per cent neurologic function scores and ranks according to iv fluid and position groups. Neurologic function was significantly worse in dextrose-pretreated monkeys at the  $P < 0.05$  level by the Mann-Whitney rank sum test. There were no significant differences according to position groups.

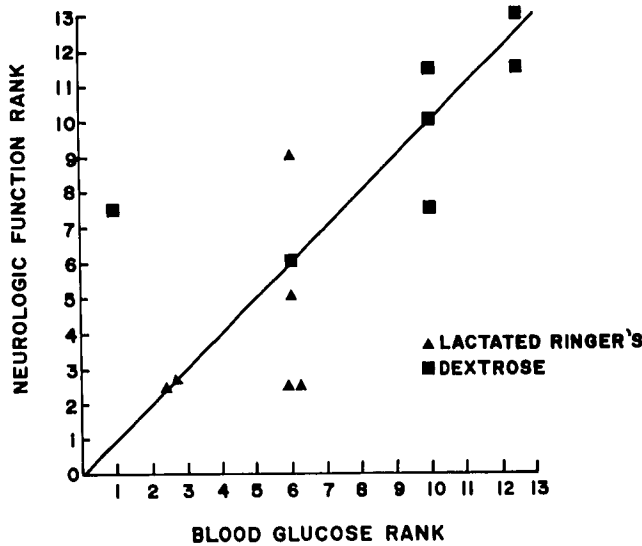


FIG. 2. Correlation between neurologic function rank (ranked from best to worst) and blood glucose rank (ranked from lowest to highest). The solid line represents the line of identity. ( $r_s = 0.76$ ;  $P < 0.005$ ). Note that there were five groupings of blood glucose rank scores. These were at blood glucose levels of 100, 120, 150, 180, and 240  $\text{mg} \cdot \text{dl}^{-1}$ , respectively.

monkeys. Blindness and ataxia were no more common in supine than prone monkeys.

There was no correlation between the rapidity of return of EEG activity postischemia and the ultimate neurologic outcome.

#### HISTOPATHOLOGY EVALUATION

Histopathologic examination revealed a pattern of pathologic changes primarily characterized by early ischemic neuronal change, ischemic neuronal necrosis, and infarction. Ischemic changes as well as infarction were usually symmetric, including the Group L monkeys. Changes at all locations were most noticeable in the gray matter. When all animals were considered as a group, the greatest histologic injury was noted in the substantia nigra, followed collectively by the hippocampus, midbrain, and cerebellar Purkinje cells, followed next by the frontal, parietal, and occipital cortex and the caudate nucleus and putamen. In contrast to the large amount of injury to structures rich in gray matter, no injury whatsoever was recorded in the central white matter, corpus callosum, and anterior commissure, which have white matter only.

When comparisons were made according to sugar history, overall histopathology scores were greater in Group D ( $101 \pm 13$  points) than Group R monkeys ( $60 \pm 3$  points;  $P < 0.05$ ) (fig. 3). When examined according to specific brain loci, the increased injury in Group D monkeys achieved statistical significance only in posterior cerebral structures, that are rich in gray matter. Injury to the in-

sular cortex, thalamus, Purkinje cells, and substantia nigra were greater in Group D than Group R at the  $P < 0.05$  level. The enhancement of posterior cerebral injury following dextrose infusion and hyperglycemia was also suggested by the fact that posterior cerebral histopathology scores were greater in Group D ( $62 \pm 7$  points) than Group R ( $31 \pm 3$  points;  $P < 0.005$ ), and there was a significant correlation between preischemic blood glucose rank and posterior histopathology rank ( $r_s = .70$ ;  $P = 0.01$ ). In contrast, anterior cerebral injury did not significantly differ between Groups D and R ( $P < 0.6$ ), nor was there a significant correlation between blood glucose and anterior histopathology ranks ( $P > 0.5$ ). The correlation between preischemic blood glucose rank and overall histopathology rank achieved significance only at the  $P = 0.07$  level.

When overall histopathology scores were analyzed according to positional groups, there were no significant differences. Regarding regional histopathology scores, significant differences between anterior and posterior or dependent and nondependent histopathology scores oc-

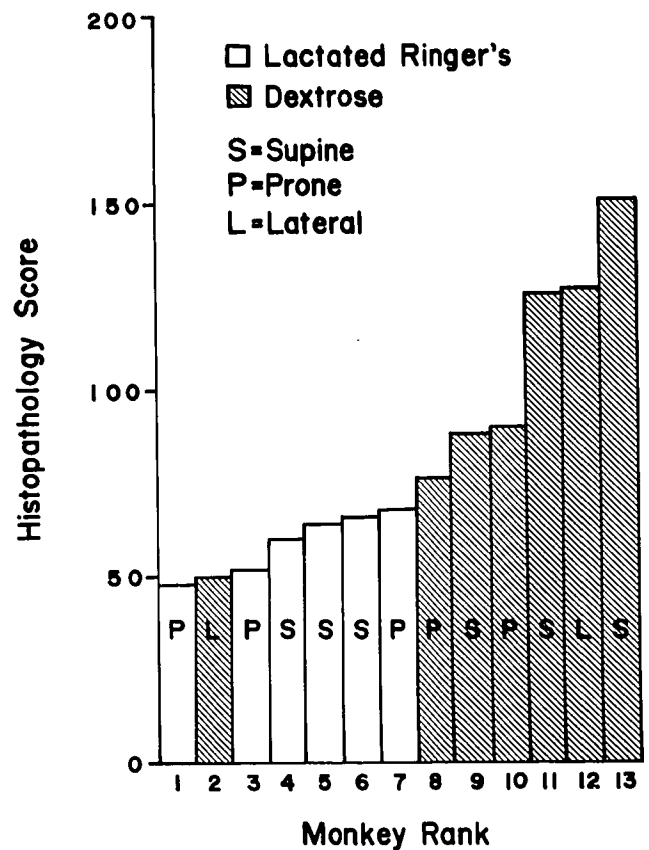


FIG. 3. Histopathology scores and ranks according to iv fluid and position groups. Histopathology scores were significantly worse in dextrose-pretreated monkeys at the  $P < 0.05$  level by the Mann-Whitney rank sum test. There were no significant differences according to position groups.

TABLE 3. Comparison of Position during Complete Cerebral Ischemia and Pattern of Histopathologic Injury

Group	n	Histopathology Scores					
		Anterior	Posterior	Significance	Dependent	Nondependent	Significance
L	2	36 ± 18	53 ± 21	—	46 ± 20	43 ± 19	—
P	5	24 ± 2	42 ± 7	*	24 ± 2	42 ± 7	*
S	6	43 ± 6	50 ± 10	NS	50 ± 10	43 ± 6	NS
All	13	35 ± 4	47 ± 6	NS	39 ± 6	43 ± 4	NS

NS = no significance.

\* Posterior cerebral areas achieved significantly greater histopathology scores ( $P < 0.05$ ) in Group P only.

curred only in prone monkeys in which posterior histopathology scores ( $42 \pm 7$  points) were significantly higher than anterior scores ( $24 \pm 2$ ;  $P < 0.05$ ) (table 3).

There was a significant correlation between neurologic function rank and histopathology rank ( $r_s = .69$ ;  $P < 0.02$ ) (fig. 4).

#### CEREBRAL GLUCOSE EVALUATION

Cerebral and blood glucose values are listed in table 4. There was roughly a three-fold increase in brain glucose and a four-fold increase in blood glucose following the infusion of 50 ml dextrose 5% in 0.45% saline solution over  $11 \pm 1$  min. Although there were significant increases in brain ( $P < 0.01$ ) and blood ( $P < 0.01$ ) glucose levels with infusion, the ratios of brain to blood glucose did not change meaningfully.

#### RADIOGRAPHIC EXAMINATION

Radiographic examination showed pooling of angiographic contrast material in posterior cerebral areas with the monkey in the supine position. The amount of pos-

terior contrast material diminished when the monkey was placed in the prone position. With the animal in the lateral decubitus position, we did not demonstrate pooling of contrast in the dependent hemisphere; however, there was difficulty in obtaining high-quality lateral decubitus angiograms.

#### Discussion

Approximately 40% of patients who are successfully resuscitated from cardiac arrests never regain consciousness and die in the hospital,<sup>9</sup> while an estimated 20% survive and have severe brain damage.<sup>21</sup> Of those regaining consciousness, many will have visual disturbances, ataxia, and tremors, suggesting injury to posterior circulation cerebral structures.<sup>22</sup> In a recent report from our laboratory,<sup>1</sup> we also noted that monkeys exposed to 17 min complete cerebral ischemia sustained the greatest injury to posterior cerebral structures. When the histopathology scores of anterior and posterior cerebral structures were compared, we found that the posterior scores ( $81 \pm 8$  points) showed worse injury than the anterior scores (45

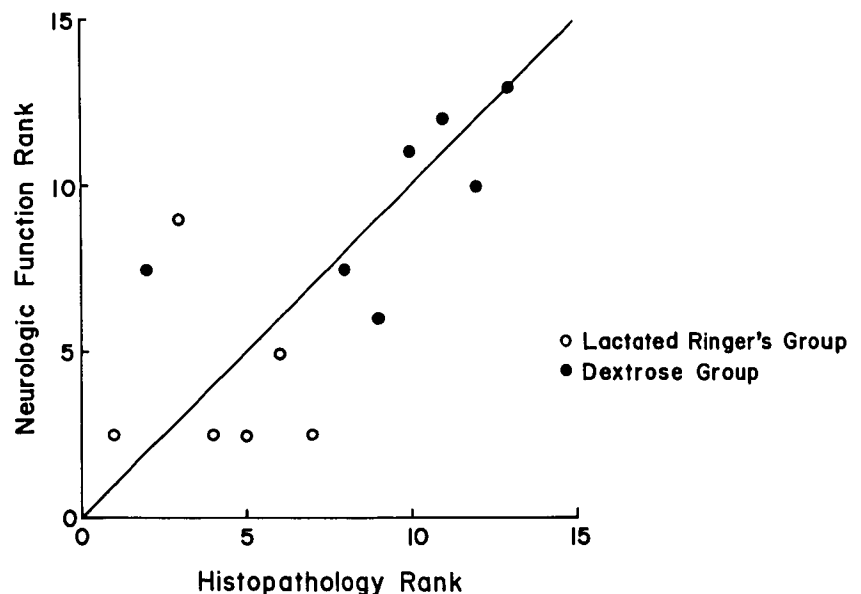


FIG. 4. Correlation between neurologic function rank and histopathology rank (ranked from best to worst). The solid line represents the line of identity ( $r_s = 0.69$ ;  $P < 0.02$ ).

TABLE 4. Changes in Blood and Brain Glucose with Dextrose Infusion

Time	Cumulative Volume D <sub>5</sub> 1/2 Normal Saline Infused	Blood Glucose (mg · dl <sup>-1</sup> )	Brain Glucose (μmol · g <sup>-1</sup> )
a	0	57 ± 8	1.64 ± 0.22
b	25 ml	193 ± 15	—
c	50 ml	244 ± 25*	5.11 ± 0.48*

Samples were taken before infusion of dextrose 5% in 0.45% saline (time "a"); after infusion of 25 ml in 6 ± 1 min (time "b"); and 3 min after infusion of 50 ml in 11 ± 1 min (time "c"). (n = 4; monkey neurologic function ranks from figure 1 were 6, 8, 12, and 13).

\* Time "c" value significantly greater than time "a" value ( $P < 0.01$ ).

± 4 points). This difference achieved a  $P < 0.001$  by unpaired *t* test (unpublished data). Because these monkeys were in the supine position during and immediately after the period of complete cerebral ischemia (as we assume is true of most cardiac arrest survivors), we hypothesized that pooling of blood in dependent areas of the brain during the period of ischemia and early resuscitation may have contributed to the regional injury.

There is some experimental evidence that suggests that areas of the brain exposed to static hypoxic blood or certain blood elements during complete cerebral ischemia sustain more damage than areas not so exposed,<sup>10-15,††</sup> and the results of those studies are summarized in a recent report from our laboratory.<sup>23</sup>

In the latter study, Stangland *et al.*<sup>23</sup> demonstrated large variations in the cranial blood content of dogs placed in the 45-degree head-up *versus* 10-degree head-down positions during periods of complete cerebral ischemia induced with aortic occlusion. Despite these differences in cranial blood content, the authors reported no difference in postischemic cerebral blood flow, cerebral metabolic rate, or neurologic outcome between the two groups. This study was limited by the fact that cerebral blood flow and metabolic rate measurements were restricted to portions of the frontal and lateral cortex, the postischemic neurologic assessment was limited in its discriminatory power, and histopathologic studies were not performed. For this reason, the current study was performed in an established primate model that includes postischemic histopathologic evaluations and allows a more sensitive postischemic neurologic examination.

Although we were able to document a pooling of contrast material within dependent cerebral structures during ischemia, we were unable to show that cerebral injury was greater in areas that were dependent at the time of complete ischemia. The only group in which histopathology scores differed between dependent and nondependent areas (Group P), showed the greatest injury to the posterior, nondependent area. These latter data directly contradict the hypothesis that blood pooling in dependent

cerebral tissue during periods of cerebral ischemia determines the pattern of regional cerebral injury.

In contrast to our inability to document alterations in neurologic injury by varying head position, our study clearly demonstrated that administration of clinically relevant doses of dextrose solution prior to cerebral ischemia augments postischemic neurologic dysfunction and histologic injury. Preliminary evidence that sugar administration prior to complete cerebral ischemia worsened neurologic outcome was reported by Myers and Yamaguchi.<sup>2</sup> These authors observed that when monkeys were exposed to 14 min of cardiac arrest, two monkeys receiving 5% glucose (approximately 35 and 70 ml · kg<sup>-1</sup>, respectively) had greater postischemic neurologic injury than four saline-pretreated monkeys. In a subsequent study from that laboratory, Myers<sup>24,25</sup> gave food-deprived monkeys intravenous glucose 2.5 or 5.0 g · kg<sup>-1</sup> and found that these monkeys had poorer postischemic neurologic function and greater cerebral perfusion defects than saline-pretreated monkeys.

The detrimental effects of increased blood glucose values on postischemic neurologic outcome has also been reported in humans. Pulsinelli *et al.*,<sup>7</sup> in a retrospective study, found that diabetic patients who developed ischemic strokes had worse neurologic outcomes and a greater incidence of stroke-related deaths than nondiabetic patients. In a prospective study, this same group of authors<sup>7</sup> reported that of 31 nondiabetic patients suffering from ischemic strokes, 14 patients with an admission blood glucose of > 120 mg · dl<sup>-1</sup> tended to have a worse neurologic outcome than 17 patients with an admission blood glucose < 120 mg · dl<sup>-1</sup> ( $P = 0.061$ ). These observations were complimented by the report of Longstreth and Inui, in which they evaluated the neurologic outcome of 430 consecutive patients who were resuscitated from out-of-hospital cardiac arrests.<sup>8</sup> All of these patients received varying amounts of glucose 5% solution *iv*. Admission blood glucose values from patients who did not awaken postarrest (341 mg · dl<sup>-1</sup>) were greater than values in patients who awakened (262 mg · dl<sup>-1</sup>;  $P < 0.0005$ ). Of patients who awakened, those having persistent neurologic deficits had greater admission blood glucose values (286 mg · dl<sup>-1</sup>) than patients without deficits (251 mg · dl<sup>-1</sup>;  $P < 0.02$ ).

Despite the large amount of data which suggests the detrimental effects of sugar administration and/or high blood glucose on postischemic neurologic outcome, these and other studies suffer from various faults of experimental design: 1) the groups are too small to show statistical significance<sup>2,7</sup>; 2) the sugar load is unknown<sup>8,9</sup>; 3) sugar administration exceeds clinically relevant doses<sup>2-4,6,25</sup>; 4) the period of ischemia is variable or unknown<sup>7-9</sup>; 5) the studies were retrospective<sup>7-9,††</sup>; 6) the subjects had coexisting disease that may have interfered with the results<sup>6-9</sup>; or 7) the animal model was



nonprimate with questionable applicability to humans.<sup>5,4,6,††</sup> Accordingly, our study was designed to eliminate many of these variables. We were able to demonstrate uniquely that after a known period of cerebral ischemia in primates, clinically relevant doses of dextrose 5% solution iv had an augmenting effect on postischemic neurologic injury, even though there were minor differences between the blood glucose values of the study groups. In agreement with the retrospective analysis of Todd *et al.*,<sup>††</sup> our findings suggest that small fluctuations in blood glucose, and more importantly brain glucose, may affect the results of neurologic-outcome studies. Small differences in preischemic brain glucose may explain the conflicting results of previously reported brain resuscitation studies.<sup>16,17,25,26</sup>

Increased cerebral injury with sugar administration prior to complete cerebral ischemia is proposed to be related to anaerobic lactate production from cerebral glucose.<sup>5,24,27,28</sup> Endogenously or exogenously induced blood glucose increases are followed by parallel increases in brain glucose.<sup>27</sup> The latter phenomenon was observed in our study. Should cerebral ischemia occur during periods in which cerebral glucose is increased, increased amounts of lactate will be produced.<sup>5,27</sup> Lactate is presumably responsible for postischemic tissue injury, whether ischemia is complete or incomplete in nature.<sup>6,24,28</sup> When glucose is administered shortly before the onset of ischemia, for a given duration of ischemia there should be proportional increases in preischemic brain glucose, postischemic cerebral lactate levels, and postischemic cerebral histologic damage.<sup>5,6,24</sup>

Decreasing blood glucose to subnormal values prior to cerebral ischemia apparently has no protective value. Siemkiewicz and Hansen<sup>3</sup> compared neurologic outcome with blood glucose in rats exposed to 10 min of complete cerebral ischemia. Control rats (blood glucose  $141 \pm 8$  mg · dl<sup>-1</sup>) had better neurologic outcomes than rats in which hyperglycemia was induced with ip injections of glucose (blood glucose  $432 \pm 9$  mg · dl<sup>-1</sup>). Outcome in rats made hypoglycemic with insulin injections (blood glucose  $34 \pm 4$  mg · dl<sup>-1</sup>) was intermediate between normoglycemic control rats and hyperglycemic rats. Furthermore, the ability of sugar administration to augment postischemic cerebral injury is apparently independent of the osmotic effect of the sugar load. Pulsinelli *et al.*<sup>4</sup> demonstrated increased postischemic cerebral histologic damage in rats given glucose pretreatment when compared with rats given saline pretreatment. Rats pretreated with mannitol had postischemic cerebral injury similar to saline-pretreated rats, even though plasma osmolality was similar in mannitol- and glucose-pretreated groups.<sup>4</sup>

There is controversy regarding the effects of postischemic sugar administration on postischemic neurologic outcome: some studies in rats show augmentation of neu-

rologic injury,<sup>5</sup> while other rat studies show no increase in injury.<sup>4,6</sup> The significance of these findings regarding the effects of postischemic administration of dextrose on the ultimate neurologic outcome in our study and similar studies<sup>1,16,17</sup> is unknown.

In the current study, preischemic dextrose infusion resulted in a significant increase in postischemic neurologic injury, even though blood glucose values immediately preischemia were not significantly greater in dextrose than lactated Ringer's solution-treated animals. This may reflect the fact that blood glucose values at ischemic onset may have underestimated the magnitude of brain glucose increases in dextrose-treated animals. Our data in four monkeys showed, as expected, that during periods of sugar infusion using volumes comparable to those used in neurologic outcome studies, there was an increase in blood glucose to  $244$  mg · dl<sup>-1</sup> accompanied by a concomitant increase in brain glucose. This increase in brain glucose is presumably due to facilitated diffusion in normal brain,<sup>28</sup> and also may be influenced by disruption of the blood-brain barrier in brain-injured subjects (such as those used in our biopsy data). At the cessation of sugar infusions, insulin release produces a decline in blood glucose to near normoglycemic levels. This process had obviously begun, but was incomplete at ischemic onset in dextrose-treated monkeys, because their blood glucose values ( $181 \pm 19$  mg · dl<sup>-1</sup>) were numerically larger than lactated Ringer's solution-treated subjects ( $140 \pm 6$  mg · dl<sup>-1</sup>), but less than the peak blood glucose values measured in brain biopsy studies ( $244 \pm 25$  mg · dl<sup>-1</sup>). As blood glucose concentrations decline, there is indirect evidence to suggest that the brain will not release excess glucose to the blood, but will instead absorb free water until brain and blood glucose concentrations equilibrate (rebound phenomenon).<sup>27,29</sup> Thus, during periods of stable blood glucose values as would be expected in Group R, blood glucose values would accurately reflect brain glucose values. However, during periods of declining blood glucose values as would be expected following sugar infusion in Group D, brain glucose decreases would lag behind blood glucose decreases, and blood glucose values would slightly underestimate brain glucose values. Thus, the brain could be at increased risk for ischemic injury following sugar infusion, even though blood glucose values were not significantly elevated in sugar-treated subjects at the time of ischemia. This theory would explain our observation that dextrose treatments resulted in enhancement of postischemic injury, even though preischemic blood glucose values were not significantly higher in Group D than Group R ( $P = 0.07$ ). If we assume that the decline in blood glucose following dextrose infusion occurred at similar rates in all monkeys, but was not complete at ischemic onset, and if we assume that the equilibration between brain and blood glucose occurred at sim-

ilar rates in all monkeys, then there should have been a large positive correlation between blood glucose rank and brain glucose rank, regardless of whether monkeys received dextrose or not. Thus, monkeys with lower blood glucose ranks would have lower brain glucose values at ischemic onset than monkeys with higher blood glucose ranks. This explanation would account for the high correlation between preischemia blood glucose rank and postischemic neurologic function rank (fig. 2).

In summary, the current study was designed to evaluate the effects that head position and dextrose administration would have on the severity and pattern of postischemic neurologic injury. Our results demonstrate that clinically relevant doses of 5% dextrose solution can augment postischemic neurologic injury, and this increase in injury is greatest in cerebral structures supplied by the posterior circulation. In contrast, altering head position to produce pooling of blood in areas of the brain that were dependent during the ischemic period did not influence either the severity or distribution of cerebral injury.

We conclude that administration of sugar-containing solutions and hyperglycemia should be avoided in all patients at risk for impending cerebral ischemia. We speculate that augmentation of postischemic cerebral injury by small increases in brain glucose may explain previous discrepancies in the literature regarding the efficacy of certain cerebral resuscitation regimens.

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