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Effects of Iso-osmolal Intravenous Fluid Therapy on Post-ischemic Brain Water Content in the Rat

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This study evaluated the effects of different iso-osmolal solutions used for intravascular volume replacement on post-ischemic cerebral edema. Fasted Sprague-Dawley rats underwent 10 min of severe (near-complete) forebrain ischemia (bilateral carotid artery occlusion and hemorrhagic hypotension). At the completion of ischemia, 40% of the estimated total blood volume was replaced by iso-osmolal saline, 6% hetastarch, or blood. Plasma osmolality remained similar between groups throughout the experiment, while saline infusion resulted in a significant but transient decrease in colloid oncotic pressure. At 1.5 h, 6 h, and 24 h post-ischemia (PI), specific gravity was determined for tissue samples taken from the hippocampus, caudoputamen, and neocortex. Normal values were obtained from rats receiving anesthesia only. The ischemic insult resulted in a significant increase in regional water content at 1.5 h PI in animals receiving blood. These values were not different from rats receiving saline or hetastarch. At 6 h PI, partial resolution of the edema was observed, with no differences in regional specific gravity occurring between fluid groups. At 24 h PI, again, no difference between fluid regimens was seen in the hippocampus or neocortex. However, in the caudoputamen, hetastarch produced a significant increase in water content relative to both saline and blood. With that exception, the authors' results indicate that early post-ischemic cerebral edema remains generally independent of iso-osmolal fluids used for resuscitation in this model of global ischemia. (Key words: Brain: edema; ischemia. Fluid balance: colloid; crystalloid. Hemorrhage. Shock.)

PATIENTS AT RISK for perioperative cerebral ischemia frequently receive large volumes of intravenous fluids (*e.g.*, for resuscitation from major hemorrhage). With respect to the brain, optimal intravenous fluid therapy under these conditions remains poorly defined. Primary requirements for minimization of neurologic injury include restitution of cerebral blood flow and oxygen delivery. Assuming that these two conditions are met, the effect of intravenous fluids on post-ischemic brain edema can be considered.

Zornow *et al.*, using a hemodiluted rabbit model, showed that water content in the uninjured brain is determined by plasma osmolality, not colloid oncotic pressure.[1] This conclusion is consistent with earlier *in vitro* studies on nervous tissue, which found that a decrease in extracellular osmolality led to net water movement into the cell, and that this flux was associated with an increase in cellular volume.[2,3] Regulation of brain water content also depends on functional integrity of the blood-brain barrier and the energy dependent Na^+-K^+-ATPase pump.[4,5] Failure of these mechanisms as sequelae of cerebral ischemia may influence normal hydrodynamics between cerebral intravascular and extravascular compartments.[6,7]

For the post-ischemic brain, there is little information concerning the effects of different types of intravenous fluids on edema formation. The purpose of this study was to determine the effects of intravascular volume replacement, with iso-osmolal crystalloid and colloid solutions, on post-ischemic brain water content. Cerebral structures known to be selectively vulnerable to ischemia[8] were evaluated subsequent to a 10-min episode of near-complete forebrain ischemia in the rat.[9,10]

Materials and Methods

With institutional Animal Research Committee approval, fasted male Sprague-Dawley rats (age range 9–10 weeks; body weight range 300–340 grams) were utilized for this experiment. Eight rats (Normal group) were anesthetized with 3.0% halothane in 30% O_2 and balance N_2O. A rapid thoracotomy was performed for aspiration of 1.3 ml of blood from the left ventricle. This required 15–20 s, and allowed measurement in duplicate of hematocrit, plasma glucose (Beckman Glucose Analyzer, Fullerton, CA), plasma osmolality (Osmette A, Precision Systems, Sudbury, MA), and colloid oncotic pressure (Colloid Osmometer 4400, Wescor, Logan, UT), thereby establishing normal values. Following blood withdrawal, each rat was immediately decapitated. The brain was rapidly removed and placed in a chamber with gloved port holes. Relative humidity within the chamber was maintained at 90% saturation by a humidifier, while the temperature was maintained at 13–15° C with ice.[11] The brain was dissected, and bihemispheric samples weighing approximately 25 mg were obtained from neocortex (gray matter), caudoputamen, and dorsolateral hippocampus. The specific gravity of these samples was measured using a Percoll® (Pharmacia, Uppsala, Sweden) linear density gradient with a sucrose concentration of 0.125 M according to

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the technique described by Tengvar *et al.*[12,13] The column was calibrated prior to the analysis of each brain using glass beads with known densities of 1.0300, 1.0350, 1.0400, 1.0450, and 1.0500 gm/cc (SGA Scientific, Bloomfield, New Jersey).

Seventy-eight rats were then prepared for forebrain ischemia as follows. Each rat was anesthetized with 3.0% halothane and 30% O_2 in N_2O, endotracheally intubated, connected to a small animal respirator, and ventilated with a mixture of 0.7% halothane in 30% O_2 and balance N_2O. Tidal volume and rate were adjusted to maintain normoxia and normocapnia. The tail artery was catheterized for monitoring of blood pressure and to sample blood. A transverse ventral neck incision was made, and the common carotid arteries were isolated under magnification, with care taken to preserve the vagus nerves and cervical sympathetic plexi. Finally, the right jugular vein was cannulated with a silicone catheter.

In the pre-ischemic interval, muscle paralysis was provided by a 1-mg intravenous bolus of succinylcholine, repeated as necessary. Heparin (50 IU) was given intravenously prior to the first blood gas measurement. Bipolar EEG recordings (Grass® Electroencephalograph, Model 8-10C; Quincy, Massachusetts) were obtained from a pair of needle electrodes inserted into the temporalis muscle on each side of the head. Rectal temperature was maintained between 36.5–37.5° C by surface heating or cooling.

Following surgical preparation, the halothane was discontinued, and each rat allowed to stabilize for 30 min. No surgical manipulation was carried out during this interval. From the tail artery catheter, 1.5 ml of blood was withdrawn for measurement of blood gases, hematocrit, plasma glucose, colloid oncotic pressure, and osmolality. Rats then underwent a 10-min period of near-complete forebrain ischemia induced by a bolus iv infusion of 3 mg (0.3 ml) trimethaphan camphor sulfonate to achieve a mean arterial pressure (MAP) of 50 ± 5 mmHg, after which both carotid arteries were clamped and a timer was started.[9] Central venous exsanguination was performed as necessary to maintain MAP at 50 ± 5 mmHg throughout ischemia. EEG was recorded to assure isoelectricity during this period. Ischemia was reversed after 10 min by simultaneous removal of the carotid artery clips and rapid restoration of intravascular volume (see below). Any animal which failed to achieve a MAP ≥ 100 mmHg within 2 min after carotid unclamping was eliminated from further analysis. All animals received 0.4 ml of 0.6M $NaHCO_3$ intravenously at termination of ischemia to counteract systemic acidosis.

Prior to ischemia, estimated total blood volume (EBV) for each rat was calculated (body weight × .06), as was that volume equivalent to 40% of EBV (EBV × .4). At termination of ischemia, this volume (40% EBV) was withheld from the blood shed during ischemia, and remaining shed blood was returned to the animal. Forty percent of EBV was chosen as the replacement volume, as this is characteristically the minimum volume aspirated during ischemia necessary to maintain hypotension. The rats were then randomly assigned to one of three groups on the basis of the intravenous fluid used to replace withheld blood: Hetastarch (n = 24) = iso-osmolal hetastarch in a volume equivalent to 40% of estimated total blood volume; Saline (n = 24) = iso-osmolal saline in a volume equivalent to three times 40% of estimated total blood volume; and Blood (n = 24) = reinfusion of all shed blood.

Blood volume already withdrawn for pre-ischemic chemistry (1.5 ml) was included in these calculations with rats in the Blood group receiving an additional 1.5 ml of blood from a fasted donor rat at the termination of ischemia. Iso-osmolal saline and hetastarch solutions were prepared, with the osmolality of each solution corrected to approximate the mean plasma osmolality of the Normal group (0.9% NaCl adjusted to 295 mOsm · kg H_2O^{-1} with 5.0% NaCl, and 6.0% hetastarch (American Critical Care, McGraw Park, IL) adjusted to 294 mOsm · kg H_2O^{-1} with sterile water).

Blood pressure was continuously monitored during the early recovery period. At 10-min intervals, the EEG was recorded. Body temperature was kept near 37° C by surface heating or cooling. After a recovery period of 25 min, 1.5 ml of arterial blood was withdrawn to repeat the laboratory panel taken prior to ischemia. This blood was replaced by an equal volume of blood taken from either a fasted donor rat (Blood group) or from blood shed during ischemia (Saline and Hetastarch groups). The arterial catheter was then removed. The neck and tail incisions were closed with sutures. Thirty minutes post-ischemia, the N_2O was discontinued, the animals regained consciousness and resumed spontaneous ventilation, and the tracheas were extubated. The animals soon became ambulatory and were then housed in cages with free access to pellet food and water.

In the post-ischemic phase, intravascular volume replacement groups were subdivided (n = 8), and gravitimetric analysis for regional brain water content was performed at either 1.5 h, 6 h, or 24 h after termination of ischemia in a manner identical to that previously described for the Normal group. At respective post-ischemic intervals, animals in each group were assessed for evidence of gross motor paresis, ability to ambulate, and for motor signs of seizure activity.

Six rats were eliminated from data analysis and replaced by the appropriate number of rats in each treat-

TABLE 1. Physiologic Values in Blood, Hetastarch, and Saline Resuscitated Animals Immediately Prior to and 2, 15, and 25 Min After Ischemia Interval

	Blood (n = 24)	Hetastarch (n = 24)	Saline (n = 24)
Pre-ischemia			
Pa_{O_2} (mmHg)	114 ± 17	115 ± 17	116 ± 23
Pa_{CO_2} (mmHg)	39.0 ± 3.7	39.7 ± 3.4	41.3 ± 3.5
Arterial *p*H	7.38 ± .03	7.37 ± .03	7.37 ± .02
Rectal temp (°C)	37.1 ± 0.3	37.2 ± 0.2	37.2 ± 0.2
Body weight (gr)	314 ± 27	303 ± 28	302 ± 22
MAP (mmHg)	121 ± 8	122 ± 6	126 ± 8
2 min post-ischemia			
MAP (mmHg)	122 ± 16	103 ± 23*	110 ± 12*
15 min post-ischemia			
MAP (mmHg)	126 ± 11	115 ± 12*	115 ± 12*
25 min post-ischemia			
Pa_{O_2} (mmHg)	126 ± 27	129 ± 23	121 ± 23
Pa_{CO_2} (mmHg)	39.8 ± 4.6	40.0 ± 3.1	38.3 ± 4.5
Arterial *p*H	7.38 ± .06	7.38 ± .03	7.34 ± .04
MAP (mmHg)	121 ± 16	111 ± 10*	111 ± 12*

Values = mean ± standard deviation.
* $P < .01$ as compared to Blood group.

ment regimen. Three rats demonstrated post-ischemic upper airway obstruction presumed secondary to traumatic tracheal intubation. One rat (Blood group) was deleted for major post-surgical hemorrhage, and two rats (Saline group) were deleted for failing to achieve a MAP > 100 mmHg by 2 min post-ischemia.

Data were analyzed by the Welch's *t* test and two-way analysis of variance (ANOVA) with post-hoc multiple comparison testing (Newman-Keuls test) where indicated by a significant F ratio to determine between- and within-group differences. Dunnett's *t* test was used to compare post-ischemic to pre-ischemic physiologic values. Significance was assumed with $P < .05$. Values are given as mean ± standard deviation.

Results

PHYSIOLOGIC VALUES

Physiologic values are presented in table 1. No differences between fluid replacement groups were seen with respect to pre-ischemic body weight, rectal temperature, arterial blood gases, or *p*H. Normocapnia and normoxia were present in all groups prior to and 25 min post-ischemia. No intergroup differences in MAP were observed 1 min prior to the onset of ischemia. At 2, 15, and 30 min post-ischemia, both the hetastarch- and saline-treated animals had significantly lower arterial blood pressure than those receiving blood ($P < .01$). In all groups, however, MAP was >100 mmHg at 2 min post-ischemia, and remained so throughout the subsequent observation period.

Table 2 lists values for plasma glucose, osmolality, and hematocrit. No difference was seen between groups with respect to plasma glucose at any interval. Plasma osmolality was unchanged from pre-ischemic values in all groups at 1.5 h and 6 h. At 24 h, osmolality was increased in the Hetastarch and Saline groups, but these values were not different from those animals receiving blood. As expected, hematocrit was reduced by approximately 40% in the Saline ($P < .01$) and Hetastarch ($P < .01$) groups, an effect which persisted through 24 h post-ischemia.

With respect to plasma colloid oncotic pressure, samples from the 1.5-h and 6.0-h groups were, unfortunately, damaged during prolonged freezer storage prior to analysis. Those values were thus discarded.

TABLE 2. Values by Replacement Group for Plasma Glucose, Osmolality, and Hematocrit Measured Prior to Ischemia and 25 Min, 1.5 h, 6 h, and 24 h Post-ischemia

	Pre-Ischemia (n = 24)	R = 25 min (n = 24)	R = 1.5 h (n = 8)	R = 6 h (n = 8)	R = 24 h (n = 8)
Osmolality ($mOsm \cdot kgH_2O^{-1}$)					
Blood	294 ± 3	298 ± 5	304 ± 5	299 ± 3	306 ± 2*
Hetastarch	294 ± 4	298 ± 5	301 ± 7	297 ± 15	306 ± 5*
Saline	293 ± 4	296 ± 5	304 ± 5	296 ± 3	299 ± 6
Plasma glucose (mg/dL)					
Blood	135 ± 16	158 ± 20	184 ± 27*	141 ± 12	161 ± 34
Hetastarch	128 ± 15	173 ± 25	189 ± 39*	154 ± 22	162 ± 14
Saline	124 ± 16	136 ± 26	190 ± 34*	156 ± 24	168 ± 17
Hematocrit%					
Blood	48 ± 2	46 ± 2	44 ± 2	45 ± 2	45 ± 3
Hetastarch	49 ± 2	27 ± 2*	26 ± 2*	28 ± 2*	31 ± 2*
Saline	48 ± 2	30 ± 2*	29 ± 2*	29 ± 2*	32 ± 2*
Colloid oncotic pressure (mmHg)					
Blood	17.2 ± 2.7	15.7 ± 1.2	—	—	17.5 ± 1.3
Hetastarch	17.1 ± 0.7	16.7 ± 0.6	—	—	17.6 ± 2.0
Saline	17.2 ± 0.8	9.0 ± 0.6	—	—	16.8 ± 0.2

R = recirculation interval. Note: n = 8 for colloid oncotic pressure values at pre-ischemia and R = 25 min.
* $P < .01$, comparing post-ischemic to pre-ischemic values.

TABLE 3. Regional Specific Gravity Values (gm/cc) by Fluid Replacement Group as Measured at 1.5 h, 6 h, and 24 h Post-ischemia

Recirculation Interval (Hours)	Region		
	Hippocampus	Neocortex	Caudoputamen
Blood			
1.5	1.0424 ± .0005†	1.0433 ± .0005†	1.0432 ± .0007
6	1.0434 ± .0003*	1.0438 ± .0005*	1.0439 ± .0006
24	1.0426 ± .0008†	1.0441 ± .0005*†	1.0432 ± .0011
Saline			
1.5	1.0423 ± .0005†	1.0432 ± .0004†	1.0424 ± .0005
6	1.0428 ± .0005*	1.0434 ± .0006*	1.0432 ± .0005
24	1.0432 ± .0003*†	1.0442 ± .0003*†	1.0431 ± .0014
Hetastarch			
1.5	1.0423 ± .0006†	1.0429 ± .0006†	1.0429 ± .0005
6	1.0430 ± .0005*	1.0440 ± .0006*	1.0439 ± .0007
24	1.0428 ± .0006*	1.0436 ± .0009*†	1.0409 ± .0025*†‡

* Significantly different from 1.5-h value; $P < .05$.
† Significantly different from 6-h value; $P < .05$.
‡ Significantly different from Blood and Saline groups at 24 h post-ischemia; $P < .01$.

Values for the 24-h groups (n = 8 per treatment regimen) were properly preserved, and are presented in table 2. Prior to ischemia, no difference between groups was seen. At 30 min post-ischemia, a decrease in the colloid oncotic pressure had been generated in the Saline group only ($P < .01$). By 24 h post-ischemia, this value had returned to pre-ischemic baseline, and could not be distinguished statistically from the Blood or Hetastarch groups.

BEHAVIOR

Evidence of motor paresis was absent in all rats. By 1.5 h post-ischemia, rats in all groups were ambulatory, which persisted throughout the 24-h interval. Gross motor seizure activity was not observed in any animal.

DENSITY MEASUREMENTS

Initial statistical analysis compared within group regional specific gravity (SpGr) values for interhemispheric differences. No differences were found; therefore, bihemispheric regional values from each animal were averaged for subsequent statistical procedures. Pooled values are presented in table 3. Welch's *t* test was used to compare regional values between the Normal group and those from the Blood group, as measured at 1.5 h post-ischemia. In all three regions, a significant decrease in SpGr was noted ($P < .01$), indicating that edema was present.

A two-way ANOVA was then performed on regional SpGr values measured post-ischemia as a function of fluid replacement regimen and recirculation interval (table 3). In the hippocampus (fig. 1), no effect of fluid replacement regimen was observed. A significant effect for time was present ($P < .001$), with rats in all three fluid groups having an increase in SpGr (*i.e.*, a decrease in water content) at 6 h post-ischemia when compared to respective 1.5-h values. At 24 h post-ischemia, the patterns within fluid groups diverged. Rats in the Blood group developed an increase in water content relative to 6-h values, while the Hetastarch group remained unchanged. In the Saline group, hippocampal water content at 24 h was slightly decreased relative to both 1.5-h and 6-h values.

In the neocortex (fig. 2), there was again no difference in regional SpGr between fluid groups at any post-ischemic interval. A main effect for time was present ($P < .001$). In the Saline group, the temporal pattern was identical to that seen in the hippocampus, *i.e.*, a progressive reduction in edema over the 24-h period. In the Blood group, SpGr was also elevated (*i.e.*, edema de-

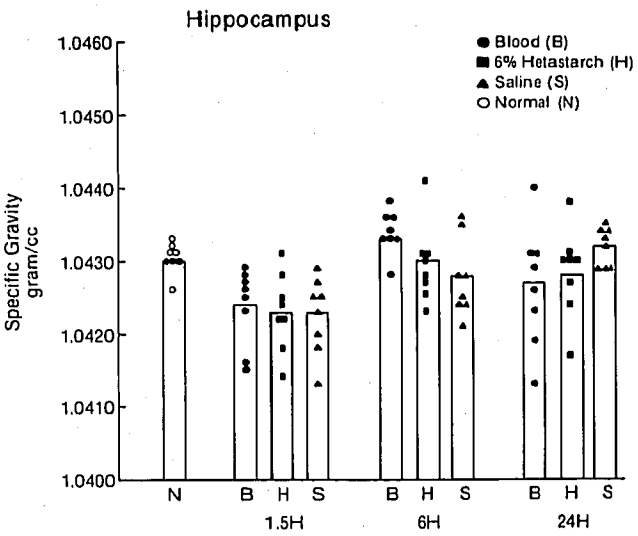

FIG. 1. Hippocampal specific gravity values as a function of fluid replacement regimen and recirculation interval (hours) post-ischemia. Each point depicts averaged regional values for one rat (n = 8 per group). Values for normal rats (N) similarly given. Bars represent mean values.

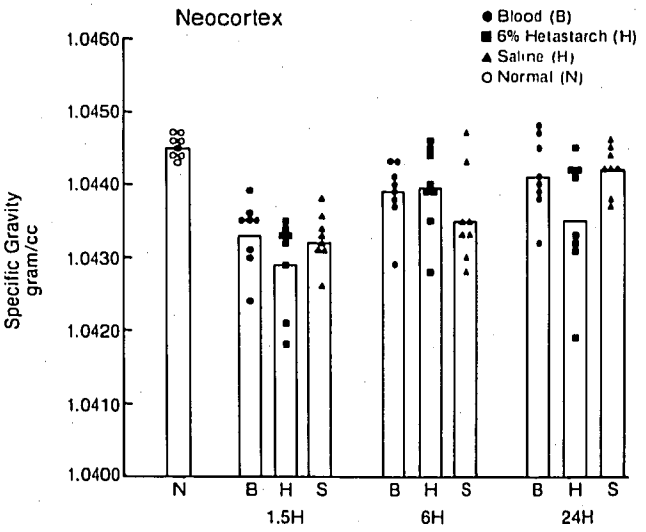

FIG. 2. Cortical specific gravity for each fluid replacement regimen as function of time (hours) post-ischemia. Each point depicts averaged regional values for one rat (n = 8 per group). Values for normal rats (N) similarly given. Bars represent mean values.

creased) at 6 h compared to 1.5 h, but remained unchanged at 24 h. In the Hetastarch group, although SpGr was elevated above 1.5-h values at both 6 h and 24 h, a significant decrease at 24 h was noted when compared to 6-h values. No interaction between fluid and time was present.

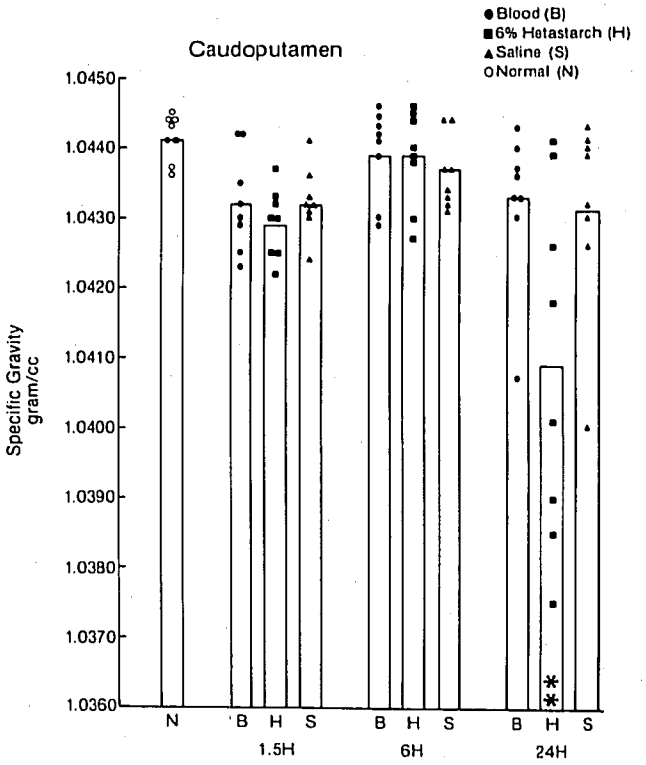

FIG. 3. Caudoputamen specific gravity as a function of fluid replacement regimen and recirculation interval (hours) post-ischemia. Each point depicts averaged regional values for one rat (n = 8 per group). Values for normal rats (N) similarly given. Bars represent mean values. $^{**}P < .01$ comparing Hetastarch to Blood and Saline groups.

In the caudoputamen (fig. 3), an interaction between fluid and time was significant ($P < .02$), as were main effects for both fluid ($P < .02$) and time ($P < .001$). By plotting mean ± SD values, it was evident that this fluid *versus* time interaction was due to the severely abberrant values measured in the Hetastarch group at 24 h. Because the standard deviation for this group was also noticeably larger than that seen in the other groups, a test for homogeneity of error variance was performed, which indicated validity in using the ANOVA. Comparing between fluid groups, no difference was noted at either 1.5 h or 6 h post-ischemia. However, at 24 h, caudoputamen SpGr in the Hetastarch group was significantly less than that measured in the Blood or Saline groups at the same interval. Although a significant main effect for time was present, only a decrease in SpGr in the Hetastarch group at 24 h relative to both 1.5-h and 6-h values reached significance ($P < .05$). A $\log_{10}$ transformation of the caudoputamen SpGr data, attempting to condense variability, provided identical results.

Discussion

Regulation of water content in normal brain reflects a complex interaction between numerous factors, including blood-brain barrier (BBB) permeability, intravascular hydrostatic pressure, cellular energy state, and plasma osmolality.[1,4,5] In the ischemically injured brain, these mechanisms may become disrupted, leading to a failure of volume homeostasis with a resultant increase in brain water content, *i.e.*, edema.[7] Our study sought to determine if iso-osmotic fluids used for major intravascular volume resuscitation differentially affect the course of ischemically induced cerebral edema.

The model used in this study was one of reversible, severe (near-complete), global ischemia.[9] Previous studies have characterized this insult to produce a reduction of blood flow in most forebrain structures to less than 5% of control, with resultant depletion of high-energy phosphates and associated EEG isoelectricity.[9] The post-ischemic (*i.e.*, reperfusion) phase has been characterized as having a transient increase in brain water content,[14] despite rapid recovery of cellular energy stores,[15] and eventual isolated cell death in selectively vulnerable regions.[10,16] BBB function and autoregulation in the post-ischemic interval have not been investigated for this model.

The results of this study confirm that an increase in regional brain water content can be identified in the early reperfusion period (1.5 h). The magnitude of this edema, however, was independent of the fluid used for major intravascular volume resuscitation, while plasma osmolality was held constant. Because saline replace-

ment of 40% of estimated blood volume resulted in a major reduction in colloid oncotic pressure in the immediate recirculation interval, it seems unlikely that colloid oncotic pressure plays a significant role in early edema formation resulting from a global ischemic insult. Similarly, hematocrit was reduced by approximately 40% in both the Saline and Hetastarch groups, but resulted in no effect on brain water content.

Because post-ischemic BBB permeability has not been characterized in this model, we can only speculate that the edema under discussion is cytotoxic in nature. Klatzo *et al.* have suggested that initial edema formation is due to intracellular energy depletion and failure of the Na^+-K^+-ATPase pump, leading to intracellular accumulation of sodium and water.[6] This is defined as cytotoxic edema, and is believed to be potentially reversible if intracellular energy is readily restored.[7] If the BBB remains intact and intravascular iso-osmolality is maintained, Na^+ and water flux into the cell should remain independent of oncotic pressure. This hypothesis is consistent with the results of our study. Edema at 1.5 h post-ischemia was independent of the colloid oncotic pressure present in the resuscitation fluids. In addition, partial resolution of the increase in brain water content was seen at 6 h post-ischemia, still remaining independent of replacement fluid.

At 24 h post-ischemia in the Blood and Saline groups, SpGr measured in the hippocampus and cortex generally conformed to a cytotoxic mechanism, *i.e.*, continued resolution of edema independent of fluid replacement regimen. The caudoputamen, however, behaved differently. Because of the significant interaction present between time and fluid regimen, results in the caudoputamen should be interpreted with caution. In the Blood and Saline groups, 24-h values were unchanged from 6-h values. However, in the Hetastarch group, a decrease in mean SpGr relative to the other groups was observed, accompanied by a wide spread in values. We are unable to interpret this observation with available information, but note that this has previously been documented in both normoglycemic and hyperglycemic rats.[14] Because colloid oncotic pressure and plasma osmolality were similar between groups by 24 h post-ischemia, it is unlikely that this event can be explained by these intravascular factors. The caudoputamen has been shown to develop microscopic evidence of neuronal necrosis earlier in the recirculation interval than either the cortex or hippocampus, suggesting a unique evolution of ischemically induced injury, which may predispose the caudoputamen to an adverse interaction with undefined intravascular constituents.[17]

In conclusion, 10 min of severe (near-complete) global ischemia produced edema in the cortex, caudoputamen, and hippocampus. This edema was most likely cytotoxic in nature, and remained generally independent of iso-osmolal fluids used for a 40% replacement of intravascular volume performed at the termination of ischemia. An exception was noted at 24 h post-ischemia in the caudoputamen, where animals receiving hetastarch had increased water content relative to those animals receiving blood or saline.

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