Anesthesiology
1998; 88:993-1002

The Effect of the Reduction of Colloid Oncotic Pressure, with and without Reduction of Osmolality, on Post-traumatic Cerebral Edema

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Background: **It has been asserted that reduction of colloid oncotic pressure (COP) can aggravate traumatic brain edema. To explore this issue, the authors measured the effect of COP reduction, with and without a simultaneous decrease in osmolality, on the development of brain edema after fluid percussion injury (FPI).**

Methods: **Isoflurane-anesthetized Wistar rats received a 2.7-atm right parasagittal FPI followed by isovolemic exchange with (1) normal saline (NS); (2) half-normal saline (0.5 NS); (3) whole blood (WB); or (4) hetastarch (Hespan, Dupont). Shed blood (16 ml) was replaced with donor erythrocytes suspended in the study fluid. The WB group received heparinized fresh donor WB. Central venous pressure was maintained with additional study fluid as required. The specific gravity (SG) of the cortex and subcortex near the impact site was determined 4.5 h after FPI. The water content of the hemispheres was also determined using the wet–dry method. To define the status of the blood–brain barrier in the non–FPI hemisphere, two additional groups (FPI, non–FPI) were studied. Both groups received 30 mg/kg Evans' blue and NS at 4 ml/kg^{-1}/h^{-1}. Four hours after FPI, the concentration of Evans' blue in the hemispheres was determined.**

Results: **After exchange, COP (mmHg ± SD) decreased in the NS (9.6 ± 2.1) and 0.5 NS (8.5 ± 0.5) groups and was unchanged in the WB (16.7 ± 3.3) and hetastarch (18.9 ± 1.1) groups. Osmolality was unchanged in the WB group (295 ± 5 mOsm/kg), increased in the NS (304 ± 3 mOsm/kg) and hetastarch (306 ± 2 mOsm/kg) groups, and was decreased in the 0.5 NS group (261 ± 6 mOsm/kg). The Evans' blue data indicated that FPI resulted in blood–brain barrier damage in both hemispheres. In all four exchange groups, the SG of both cortical and subcortical tissue was less (indicating greater water content) in the impact hemisphere than in the nonimpact hemisphere. The SG was less in both hemispheres, although it was less in both hemispheres in the NS and 0.5 NS groups than in the WB and hetastarch groups. The lowest SG values were observed in the 0.5 NS group. The wet–dry water content determinations yielded a similar pattern of edema formation.**

Conclusions: **These data, while confirming the important edematogenic effect of decreased osmolality, indicate that COP reduction *per se* can also aggravate brain edema after a mild to moderate mechanical head injury. (Key words: Cerebral edema; fluid percussion injury; fluid resuscitation; head injury; osmolality; trauma.)**

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Received from the Department of Anesthesia, University of California, San Diego; the Anesthesia Service, Veterans Affairs Medical Center, San Diego; and the Department of Anesthesiology, Loma Linda University School of Medicine, Loma Linda, California. Submitted for publication February 18, 1997. Accepted for publication November 17, 1997. Supported by National Institutes of Health grant R29-GMS2098-01A1 (to Dr. Patel), The Anesthesia Foundation of the Department of Anesthesia of the University of California, San Diego, and by a grant from the Dupont Company. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 19-23, 1996.

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SINCE the early years of this century, scientists have known that parenteral fluid administration can influence cerebral edema. Many experiments, the first performed as early as 1919, confirmed that fluid regimens that provide free water, and cause a concomitant reduction in serum osmolality, can cause cerebral edema.[1] As a consequence, the use of fluid management regimens that avoid excess free water has been a standard element of neuroanesthetic management.

Although it is accepted that a reduction in serum osmolality will cause cerebral edema, there is not uniform agreement about the potential effect of reductions in colloid oncotic pressure (COP). Can a reduction in COP without a simultaneous decrease in serum osmolality aggravate cerebral edema? Some clinicians believe fervently in the edematogenic effect of reduced COP that can occur, for instance, with the administration of large

volumes of normal saline. Furthermore, there are peer-reviewed scientific reports purporting to provide evidence for an edematogenic effect of decreased COP (see Discussion section). However, several of those reports have methodologic and other limitations that leave some uncertainty. In addition, some carefully conducted investigations have systematically sought an edematogenic effect of COP reduction but have failed to identify one.[2,3] There is an additional limitation of several previous investigations. Many studies, some confirming and some refuting an edematogenic effect of isolated COP reduction, have used a freeze lesion.[3,4] Although freeze lesions provides an excellent model of vasogenic edema, there is little confirmation that it is a valid paradigm of head injury–associated edema. The present experiment was undertaken to define the effects of isolated reduction of COP using a model of mechanical head injury, fluid percussion, that should provide a better analogy of clinical head injury than the freeze lesion.

Materials and Methods

The study was undertaken after review and approval by the local institutional animal care and use committee. Male Wistar rats weighing 436–501 g were studied. Solid food was withheld for 12 h before the study. *Ad libitum* access to water was permitted. Anesthesia was induced in a plexiglass chamber by administering 4% isoflurane. After intubation of the trachea, anesthesia was maintained with isoflurane in oxygen. The inspired concentration of isoflurane was varied from 2–3% to maintain mean arterial pressure (MAP) at 75–120 mmHg. The rats were ventilated mechanically to maintain a partial pressure of carbon dioxide in arterial blood (Pa_{CO_2}) of 35–40 mmHg. Cannulas were placed in the tail artery (PE-50), the right femoral vein (PE-50), and the right external jugular vein (PE-60). The tip of the latter was advanced to lie within the thorax. A thermistor was inserted under the temporalis muscle and pericranial temperature was servo-controlled to 37°C using a heat lamp. The animal's head was placed in a stereotaxic frame (David Kopf, Tujunga, CA). The head was shaved and, after infiltration of the scalp with 0.25% bupivicaine, a midline incision was made. The skull was exposed bilaterally. Using a 4-mm trephine, a craniectomy was made centered 5 mm to the right of the sagittal suture and 5 mm caudal to the coronal suture. Care was taken to avoid perforation of the dura. A conical plastic connector was secured in the craniectomy using light-cured dental cement (Sun-Schein; Henry Schein, Port Washington, NY). The connector was filled with saline and the nozzle of the fluid percussion device was attached to it with a three-way stopcock interposed. The stopcock was open to the atmosphere during the connection maneuver to prevent a pressure transient.

At the conclusion of the surgical preparation, blood was collected and analyzed to determine Pa_{CO_2}, partial pressure of oxygen in arterial blood (Pa_{O_2}), arterial *p*H, hematocrit, plasma glucose, serum osmolality (Vapor Pressure Osmometer Model 5500, Wescor Inc., Logan, UT), and serum COP (Colloid Osmometer model 4400, Wescor). Central venous pressure, MAP, and heart rate were recorded. The hemodynamic data were recorded again 5 min after fluid percussion injury (FPI), immediately after fluid exchange, and 2 and 4 h after exchange. Arterial blood gas determination was repeated immediately after fluid exchange, and 2 and 4 h after exchange. The COP and osmolality determinations were performed at three intervals: before exchange, immediately on completion of the exchange, and 4 h after exchange.

After the recording of baseline physiologic data, the inspired isoflurane concentration was reduced to 0.8%. Ten minutes later, a 2.7-atm fluid percussion impact was delivered using a fluid percussion device (Biomedical Engineering Division, Virginia Commonwealth University, Richmond, VA) equipped with a rodent adapter available from the manufacturer. Thereafter, isoflurane was increased to 1.5–2% as indicated by MAP. Shortly after the impact, the FPI device was disconnected and the conical connector was removed from the skull. The dura was inspected. If the dura was not intact, the animal was excluded from further study. The animal was then removed from the stereotaxic frame and placed in a prone position for the duration of the experiment. At this point, the animal was randomized to one of four fluid management regimens: whole blood, normal saline, half-normal saline, and hetastarch. The management of the groups was as follows.

Normal Saline (n = 6)

Three milliliters of arterial blood was withdrawn slowly. The same volume of heparinized donor blood was centrifuged and the plasma was removed with a pipette and discarded. The donor erythrocytes were resuspended in a volume of normal saline (Baxter Healthcare Corp., Deerfield, IL) twice that of the discarded plasma. The resuspended cells were then admin-

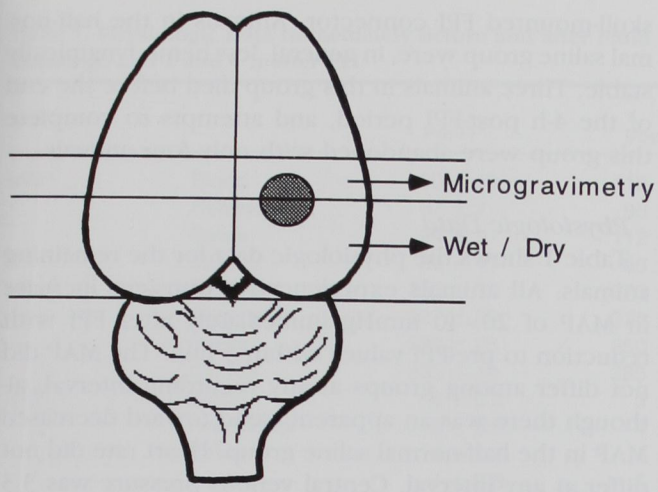

Fig. 1. Dorsal view of the rat brain indicating planes of sections relative to the fluid percussion impact site. The specific-gravity specimens were taken from the coronal section defined by the middle and rostral planes. Brain tissue between the middle and caudal planes was used for the wet–dry determination of water content.

istered intravenously to the study animal. This process was repeated until the total volume shed in 1- to 3-ml aliquots equaled 16 ml. During the exchange, additional saline was administered as required to maintain the central venous pressure at the baseline level. When central venous pressure restoration was insufficient to support MAP, phenylephrine was administered by infusion as required to maintain MAP >75 mmHg. Fluid exchange was complete within 45 min. Thereafter, additional saline was administered as required to maintain central venous pressure at the baseline level for a total of 4 h after the FPI.

Half-normal Saline (n = 4)

The fluid exchange and MAP management in the half-normal saline (Baxter Healthcare) group were done in the same manner as in the saline group.

Hetastarch (n = 6)

The management was similar to the normal saline group with the exception that the discarded plasma was replaced with an equal volume of 6% hetastarch (Hespan, Dupont Pharma, Wilmington, DE) rather than twice the volume.

Whole Blood (n = 6)

Blood was similarly withdrawn from the experimental animal in 1- to 3-ml aliquots and replaced with an equal volume of fresh, heparinized processed blood withdrawn from isoflurane-anesthetized donors.

At the end of the fourth hour after FPI, the animal was killed by decapitation. The brain was harvested rapidly and immersed immediately in cold kerosene for 10 min. It was then placed on a cold metal tray and divided coronally along three planes (fig. 1). The most rostral plane was 2 mm rostral to the center of the FPI impact site and the second passed through the center of that site. The third plane was at the caudal edge of the occipital lobes and the brain tissue posterior to it was discarded. The brain between the second and third planes was divided along the midline and the two brain fragments were weighed immediately and then incubated at 60°C for 72 h. Total water content was determined by the wet-dry method.

The 2-mm brain section defined by the first and second coronal planes remained on the cold metal tray. Three 1-mm punch biopsy specimens were collected from each hemisphere as indicated in figure 2. The two cortical biopsy sites straddled the point of FPI impact, and the subcortical site was in the dorsolateral striatum adjacent to the lateral ventricle and immediately beneath the impact site. Promptly on harvesting, these punch biopsy specimens were placed in a kerosene-bromobenzene column to determine specific gravity by the method of Marmarou *et al.*[5]

In the 10-min interval during kerosene chilling of the brain, specimens of rectus abdominis muscle and mesentery were harvested. The water content of these spec-

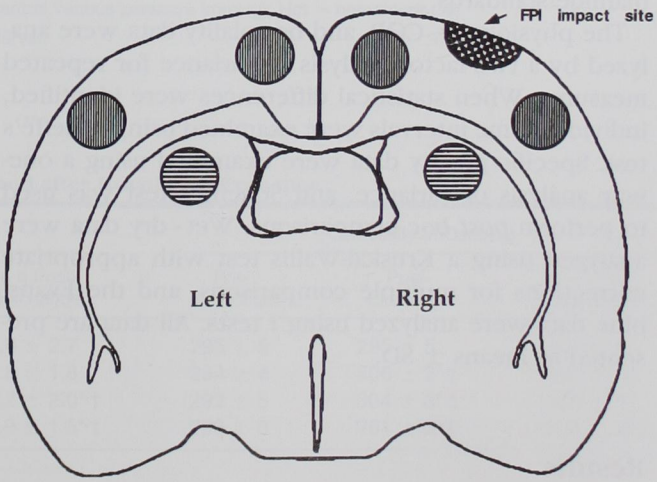

Fig. 2. A coronal brain section showing the location of the biopsy sites for specimens of cortical and subcortical tissue to determine specific gravity by microgravimetry.

imens was determined using the wet-dry method (for 72 h at 60°C).

An additional component of the investigation was performed, on a *post hoc* basis, to determine whether FPI caused blood-brain barrier (BBB) abnormality in the hemisphere contralateral to the impact site. Ten additional rats were studied. Surgical preparation was the same as described in the preceding section. In five rats, FPI was performed as described before. Five additional "sham" rats underwent identical preparation, including attachment of the fluid percussion device, but they did not receive FPI. Five minutes before the time of FPI, all rats received 1 ml/kg 3% Evans' blue (Sigma Chemical Co., St. Louis MO) intravenously. No volume exchange occurred. Maintenance fluid (normal saline) was administered at 4 $ml/kg^{-1}/h^{-1}$. Four hours after FPI, the sternum was opened, the descending aorta was clamped, and the animal was killed by transcardiac perfusion with 60 ml normal saline. The brain was removed and immersed in cold kerosene for 10 min. A 2-mm coronal section with its rostral surface 2 mm anterior to the FPI impact site was prepared exactly as described before and as indicated in figure 1. The section was divided into left and right halves and a formamide extraction of Evans' blue was performed as described by Cole *et al.*[6] Each brain section was immersed in 100 ml formamide (Fisher Scientific, Los Angeles, CA) per 100 g tissue. Seventy-two hours later, the absorbance of light at 620 nm by the supernatant was determined spectrophotometrically (Hitachi U-2000; Hitachi Ltd., San Jose, CA). The concentration of Evans' blue in the supernatant was determined by reference to Evans' blue/formamide standards.

The physiologic, COP, and osmolality data were analyzed by a two-factor analysis of variance for repeated measures. When statistical differences were identified, individual time intervals were examined using Scheffé's test. Specific gravity data were examined using a one-way analysis of variance, and Scheffé's test was used to perform *post hoc* comparisons. Wet-dry data were analyzed using a Kruskal-Wallis test with appropriate corrections for multiple comparisons, and the Evans' blue data were analyzed using *t* tests. All data are presented as means ± SD.

Results

Four animals were excluded and replaced because of dural perforation that was evident after removal of the skull-mounted FPI connector. Animals in the half-normal saline group were, in general, less hemodynamically stable. Three animals in this group died before the end of the 4-h post-FPI period, and attempts to complete this group were abandoned with only four animals.

Physiologic Data

Table 1 shows the physiologic data for the remaining animals. All animals experienced a transient increase in MAP of 20-40 mmHg immediately after FPI with reduction to pre-FPI values within 5 min. The MAP did not differ among groups at any recording interval, although there was an apparent trend toward decreased MAP in the half-normal saline group. Heart rate did not differ at any interval. Central venous pressure was 3.3 to 4.8 mmHg in all groups at all intervals. The fluid volumes (in milliliters) administered were 31.7 ± 2.5 saline; 45.5 ± 6.4 half-normal saline; 19.4 ± 0.7 hetastarch; and 19.2 ± 1 whole blood. The Pa_{O_2} and *p*H were significantly greater in the whole blood group than in the other three groups at the 4-h post-FPI measurement interval. Phenylephrine was required in two of six rats in the whole blood group, in one of six in the hetastarch groups, in five of six in the normal saline group, and in four of four rats in the half-normal saline group.

Colloid Oncotic Pressure and Osmolality

Colloid oncotic pressure and serum osmolality varied as intended by the protocol (table 2). Specifically, COP decreased significantly in the saline and half-normal saline groups. Osmolality decreased in only the half-normal saline group. In addition, osmolality increased by a small but significant amount in both the saline and hetastarch groups. This is consistent with the osmolarities of those solutions, 308 and 310 mOsm/l, respectively.

Water Content of Muscle and Mesentery

There was a significantly greater water content in both the muscle and the mesentery of the saline and half-normal saline groups than in the whole blood and hetastarch group animals (fig. 3). The muscle in the half-normal saline group had a greater water content than that in the saline group.

Brain Water Content

For each of the four groups, the water content (wet-dry method) of the impact (right) hemisphere was significantly ($P < 0.0001$) greater than that of the nonim-

Table 1. Physiologic Data Immediately before and after Fluid Percussion Injury (FPI), at the Completion of the Isovolemic Exchange and 2 and 4 h after FPI

		Pre-FPI	Post-FPI	Post-Exchange	2 h Post-FPI	4 h Post-FPI
MAP	Blood	90 ± 12	112 ± 22	103 ± 26	97 ± 18	96 ± 21
	Hetastarch	87 ± 7	96 ± 15	89 ± 13	96 ± 9	84 ± 7
	Saline	94 ± 9	112 ± 20	108 ± 6	103 ± 15	92 ± 5
	0.5 NS	89 ± 11	90 ± 7	80 ± 7	80 ± 11	80 ± 14
HR	Blood	355 ± 38	370 ± 35	365 ± 51	373 ± 41	347 ± 43
	Hetastarch	327 ± 50	373 ± 52	364 ± 57	350 ± 48	363 ± 32
	Saline	320 ± 25	350 ± 28	377 ± 20	367 ± 39	352 ± 48
	0.5 NS	335 ± 19	385 ± 19	375 ± 25	370 ± 20	352 ± 15
CVP	Blood	3 ± 0.8	3 ± 1.3	3 ± 1.2	4 ± 0.6	4 ± 0.4
	Hetastarch	5 ± 0.5	4 ± 1.0	4 ± 1.3	5 ± 1.6	4 ± 0.8
	Saline	4 ± 1.2	4 ± 1.0	5 ± 1.5	4 ± 1.0	4 ± 0.4
	0.5 NS	4 ± 0.8	5 ± 1.6	5 ± 1.3	4 ± 0	4 ± 0.9
Hct	Blood	40 ± 3	—	—	—	36 ± 2
	Hetastarch	38 ± 2	—	—	—	36 ± 2
	Saline	40 ± 2	—	—	—	34 ± 2
	0.5 NS	39 ± 1	—	—	—	34 ± 3
*p*H	Blood	7.41 ± .02	—	7.35 ± .05	7.35 ± .05	7.36 ± .04*
	Hetastarch	7.38 ± .03	—	7.33 ± .03	7.33 ± .03	7.31 ± .03
	Saline	7.41 ± .04	—	7.35 ± .05	7.33 ± .04	7.31 ± .02
	0.5 NS	7.35 ± .05	—	7.33 ± .02	7.30 ± .02	7.30 ± .01
Pa_{O_2}	Blood	172 ± 26	—	157 ± 16	160 ± 19	170 ± 17*
	Hetastarch	162 ± 12	—	152 ± 7	152 ± 11	140 ± 12
	Saline	147 ± 12	—	159 ± 3	153 ± 26	132 ± 22
	0.5 NS	161 ± 41	—	136 ± 7	132 ± 9	131 ± 11
Pa_{CO_2}	Blood	38 ± 2	—	38 ± 1	37 ± 1	38 ± 2
	Hetastarch	36 ± 1	—	38 ± 3	37 ± 1	38 ± 2
	Saline	36 ± 2	—	38 ± 2	37 ± 2	37 ± 5
	0.5 NS	37 ± 1	—	35 ± 3	37 ± 3	39 ± 2
Glucose	Blood	107 ± 12	—	—	—	—
	Hetastarch	103 ± 11	—	—	—	—
	Saline	109 ± 7	—	—	—	—
	0.5 NS	98 ± 13	—	—	—	—

MAP = mean arterial pressure (mmHg); HR = heart rate (beats · min^{-1}); CVP = central venous pressure (mmHg); Hct = hematocrit (%).

* Significant difference from the other three groups at the same measurement interval.

Table 2. Colloid Osmotic Pressure and Serum Osmolality before and after Isovolemic Exchange

	Colloid Osmotic Pressure (mmHg)			Osmolality (mOsm/kg)		
	Pre-Exchange	Post-Exchange	4 h Post-Exchange	Pre-Exchange	Post-Exchange	4 h Post-Exchange
Whole blood	18.9 ± 0.9	16.7 ± 3.3	17.0 ± 2.7	295 ± 5	295 ± 5	294 ± 8
Hetastarch	18.8 ± 1.1	18.9 ± 1.1	16.8 ± 1.8	294 ± 4	306 ± 2*‡	302 ± 4*
Normal saline	18.7 ± 3.4	9.6 ± 2.1*†	11.2 ± 2.0*†	292 ± 5	304 ± 3*‡	302 ± 4*
½ normal saline	17.6 ± 0.5	8.5 ± 0.5*†	9.9 ± 1.5*†	293 ± 6	261 ± 6*§	264 ± 4*§

* Significant difference *versus* the respective pre-exchange value.

† Significant difference *versus* the whole blood and hetastarch groups at the same interval.

‡ Significant difference *versus* the whole blood group at the same interval.

§ Significant difference *versus* the whole blood, hetastarch, and normal saline groups at the same interval.

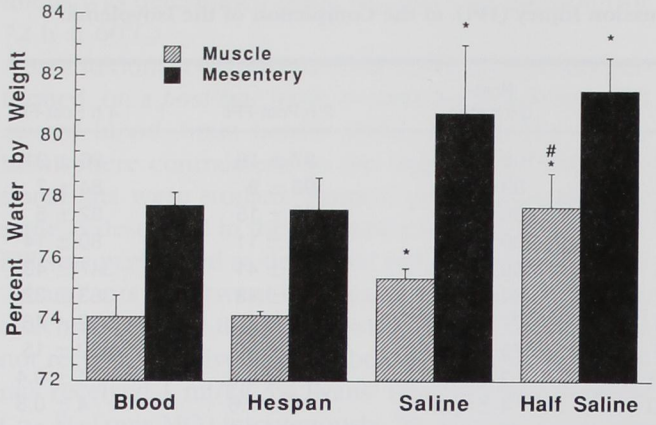

Fig. 3. The percentage water content (mean ±SD) of muscle and mesentery (wet–dry method) in animals that underwent isovolemic exchange with whole blood, hetastarch, normal saline, or half-normal saline. *$P < 0.05$ *versus* the corresponding tissue in the whole blood and hetastarch groups. #$P < 0.05$ *versus* the normal saline group.

pact (left) hemisphere (fig. 4). For both the impact and the nonimpact hemispheres, the water content was significantly greater in the saline and half-normal saline groups than in the whole blood and hetastarch groups. The whole blood and hetastarch groups did not differ. The saline and half-normal saline groups did not differ, although there was an apparent trend toward a greater water content in the half-normal saline group.

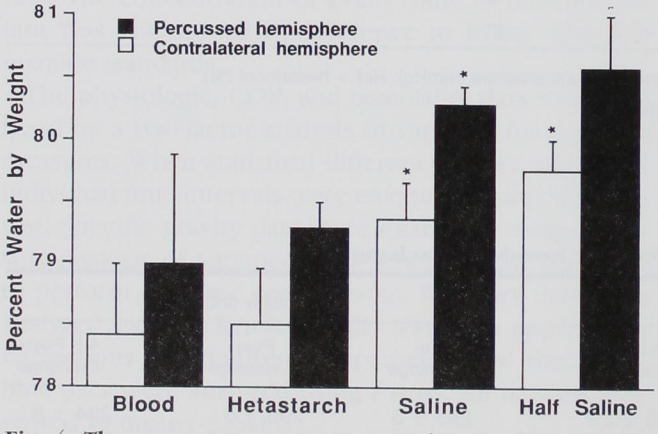

Fig. 4. The percentage water content (mean ±SD; wet–dry method) of the percussed (*right*) hemisphere and in the contralateral (*left*) hemisphere in animals that underwent isovolemic exchange with whole blood, hetastarch, normal saline, or half-normal saline. Within each group, the water content of the percussed hemisphere was greater than the water content of the contralateral hemisphere. *$P < 0.05$ *versus* the corresponding hemisphere in the whole blood and hetastarch groups.

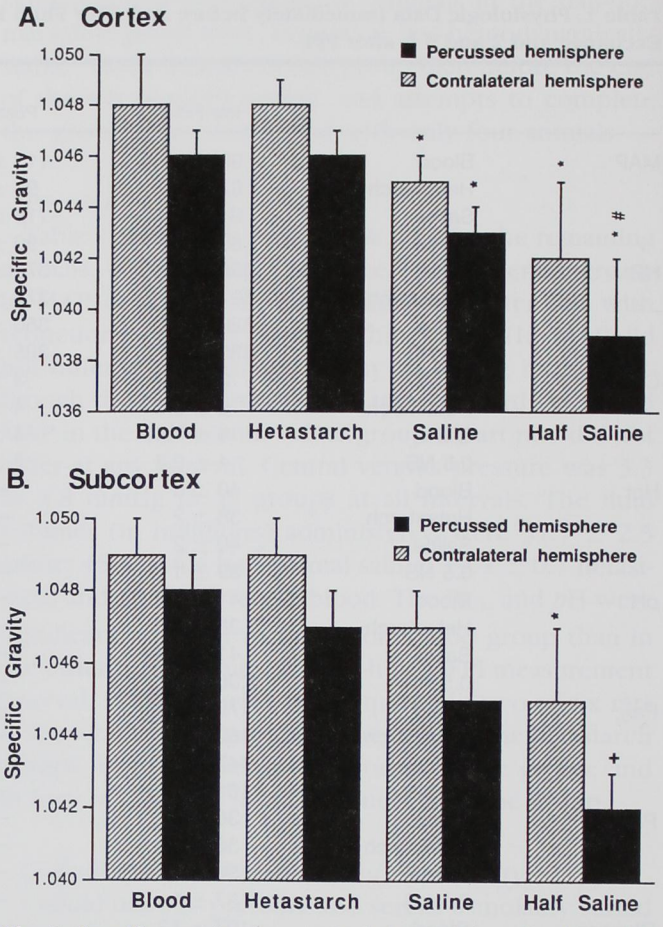

Fig. 5. Specific gravity for cortical tissue (*A*) and subcortical tissue (*B*) from the percussed (*right*) and contralateral (*left*) hemispheres in animals that underwent isovolemic exchange with whole blood, hetastarch, normal saline, or half-normal saline. *$P < 0.05$ *versus* the corresponding hemisphere in the whole blood and hetastarch groups. #$P < 0.05$ *versus* the corresponding hemisphere in the normal saline group. +$P < 0.05$ *versus* the corresponding hemisphere in the whole blood, hetastarch, and saline groups.

Brain Specific Gravity

The data presented for cortical specific gravity (fig. 5A) were obtained by averaging the specific gravities of the two cortical specimens obtained from each hemisphere. Within each of the four groups, the specific gravity of both cortical and subcortical tissue was less (indicating greater water content) in the impact hemisphere than in the nonimpact hemisphere.

Cortex

In both hemispheres, specific gravity was significantly less in the saline and half-normal saline groups than in

the corresponding hemisphere of the whole blood and hetastarch groups. The latter two did not differ (fig. 5A). Specific gravity was significantly less in the half-normal saline group than in the saline group in the impact hemisphere but not in the nonimpact hemisphere.

Subcortex

For the impact hemisphere, specific gravity was significantly less (*i.e.*, there was more water) in the half-normal saline group than in the other three groups (fig. 5B). For the contralateral hemisphere, specific gravity was significantly less in the half-normal saline group than in the whole blood and hetastarch groups. There was an apparent, but not statistically significant, trend toward lesser specific gravity values in the saline group than in the blood and hetastarch groups.

Evans' Blue

In the sham group (in which the animals underwent placement of the FPI device but did not sustain an impact), the concentrations of Evans' blue eluted from the left and right hemispheres were small and equivalent (right, 0.29 ± 0.08; left, 0.28 ± 0.13 μg/ml). In the group that did sustain an impact, the concentrations of Evans' blue were greater than in the sham animals for both the impact hemisphere (4.11 ± 1.53 *vs.* 0.29 ± 0.08 μg/ml; $P = 0.0005$) and the nonimpact hemisphere (0.86 ± 0.45 μg/ml *vs.* 0.28 ± 0.13; $P = 0.022$).

Discussion

The seminal observation of this study is that animals that received a large volume of normal saline (thus decreasing COP but not osmolality) after an FPI had a greater brain water content than did animals that received colloid or whole blood. This observation indicates that a decrease in colloid osmotic pressure *per se* without a simultaneous reduction in osmolality does have the potential to aggravate cerebral edema.

Although some clinicians have long believed that iso-osmolar crystalloids aggravate brain edema, the many attempts to demonstrate this phenomenon experimentally[2-4,7-10] have not yielded scientifically convincing proof or have generated negative results. With respect to the latter, Kaieda *et al.*[2,3] performed meticulous experiments in rabbits in which fluid manipulations were performed after a freeze lesion of the cortical surface. Using an isovolemic exchange method, they reduced COP and sampled the brain at multiple distances from the lesion's center. The intent of the protocol was to find brain regions with injury of intermediate severity in which COP reduction might have the potential to influence fluid accumulation. They could identify no such regions and concluded that reduced COP was not sufficient to aggravate cerebral edema. Shapira *et al.*[10] submitted rats to a cranial weight drop injury followed by administration of large volumes of either normal saline or 5% dextrose. Edema accumulation in the injured hemisphere was not increased by either normal saline or dextrose relative to injured but non-fluid-treated control animals. Tranmer *et al.*[4] performed a freeze lesion in dogs followed by volume loading with normal saline. They reported an increase in intracranial pressure relative to colloid-treated animals, but their brain edema measurements (wet-dry method) revealed no difference in edema accumulation in the two hemispheres. Go *et al.*[7] measured the water content of brain 1 h after a freeze lesion in rats given 0.53 l/kg normal saline during the 18 h before injury. Water content was greater in the injured cortex of saline-treated than in untreated controls. However, baseline osmolality was remarkably high (329 mOsm/kg) and was significantly reduced in the saline-treated animals, leaving the possibility that the increased edema was a function of reduction of osmolality rather than COP. Korosue *et al.*[9] studied dogs that had focal cerebral ischemia. During temporary middle cerebral artery occlusion, they performed isovolemic hemodilution with lactated Ringer's solution or low molecular weight dextran. Infarct volume 7 days later was greatest in the animals that received lactated Ringer's solution. They concluded that the decrease in COP after administration of lactated Ringer's solution was "one of the most important reasons for its detrimental effect." However, we cannot accept this study as definitive proof of an edematogenic effect of iso-osmolar crystalloids for several reasons. The first is that the authors did not measure brain edema. Second, as the authors acknowledged, lactated Ringer's solution is not iso-osmolar with respect to plasma, and its administration was associated with a significant reduction in osmolality. Finally, the nature of the BBB injuries caused by ischemia and trauma probably differ substantially, and results derived in the setting of focal cerebral ischemia might not necessarily be relevant to the setting of trauma, in which the issue of the edematogenic effect of crystalloids arises most frequently.

A priori, it seems reasonable to suspect that a BBB injury of intermediate severity might result in a func-

tional pore size between cerebral endothelial cells similar to that in many peripheral capillary beds. In the periphery, where most ionic solute can leave the capillary freely, COP reduction is associated with edema formation, as we observed in muscle and mesentery. Why, then, have previous experiments performed with mechanical head injury or freeze lesions failed to demonstrate a cerebral edematogenic effect of COP reduction? There may be several contributing factors. First, the elastance of the brain's interstitial space (*i.e.*, the interstitial pressure increase caused by a given volume increment) is greater than that of most peripheral tissues. An interstitial pressure increase results in a hydrostatic gradient that opposes further fluid movement into the tissue, and the net movement of fluid that might occur as a result of the very small transmembrane gradients that can be created by COP changes is probably very small. Accordingly, COP-related fluid movement in brain may be smaller and therefore harder to identify than in peripheral tissue. The second and greater part of the explanation may reside in the nature and severity of the insults delivered and the concomitant extent of injury to the BBB. Freeze lesions produced by cold applications of typical duration result in immediate and very substantial permeability of the BBB as indicated by extensive Evans' blue extravasation. Because of the normal movement of edema fluid through white matter toward the ventricles, brain tissue surrounding the lesion's center may already contain a substantial volume of migrating edema fluid. This may make it difficult for the small COP-driven changes that might be expected to occur in areas of intermediate injury near a freeze lesion to be manifest.

With mechanical injuries that are sufficiently severe, it may be difficult for COP-related forces to make the edema worse. This is likely to have been the case in the experiment of Shapira *et al.*[10] described earlier. It is well established that the administration of free water (given in the form of D5W in their experiment) produces edema in even normal brain.[1,11] However, in their experiment, there was no significant difference between the water accumulation in the injured hemisphere of animals that received D5W compared with those that received normal saline, suggesting that the effect of the edema consequent on the initial injury was sufficiently severe to allow little latitude for aggravating effects.

Because of our concern that earlier investigations may have involved insults of excessive severity, our preliminary investigations began with a "titration" of the FPI to identify an impact intensity that resulted in consistent but comparatively subtle (by comparison with freeze injury) penetration of Evans' blue into brain parenchyma. The 2.7-atm impact ultimately used in the present investigation resulted in faint Evans' blue staining in the cortex in the immediate vicinity of the impact site and in the dorsolateral striatum immediately inferior to the impact site.

In the present experiment, both wet-dry and microgravimetric measures of edema formation were used. The wet-dry measurement of water content was included because of the concern that, despite our preliminary efforts, the tissue sampled for microgravimetry might inadvertently have been from brain that was too severely injured for potentially small COP-related effects to be evident. The wet-dry method allowed inclusion of broader regions of the brain, including tissue at a greater distance from the lesion's center. However, the sampling method for the wet-dry determinations deliberately excluded brain regions remote from the injury site to avoid "diluting out" evidence of edema accumulation by the inclusion of large segments of normal brain.

The quantitative Evans' blue determinations reported herein were conducted on a *post hoc* basis. This phase of the investigation was performed as a consequence of the observation that normal saline administration was also associated with significantly greater edema accumulation in the hemisphere contralateral to the injury. In our preliminary experiments, gross inspection had revealed no Evans' blue leakage in the contralateral hemisphere. The initial assumption had been that the contralateral hemisphere was not sustaining an injury. The Evans' blue investigation was performed to determine whether increased BBB leakage was, in fact, occurring in the contralateral hemisphere. This investigation confirmed that such leakage was occurring, indicating that the percussion shock, as has been shown to occur with a weight drop impact effect,[12] was being transmitted across the midline and producing a BBB injury in the contralateral hemisphere.

Edema accumulation in the animals that received whole blood and hetastarch was not different. This is consistent with the fact that neither regimen caused a reduction in either COP or osmolality. However, it has been proposed that certain starch solutions may have an independent BBB sealing effect.[13,14] Edema reduction consistent with such an effect has been observed in the setting of temporary focal cerebral ischemia.[15] However, it was not evident in a model of global cerebral

ischemia with reperfusion.[16] This proposed effect, which might be anticipated to lessen edema accumulation, was similarly not apparent in the results of the present study.

The fluid-exchange protocol resulted in increases in osmolality in both the saline and hetastarch groups. These increases are in keeping with the osmolality of these solutions, both approximately 310 mOsm/kg. An osmotically mediated dehydration of the brain might be anticipated in these two groups but was not evident in the data. It is possible that the gradient that occurred was insufficient to cause differences detectable using the present methods. However, it is more likely, given the small size of the molecules responsible for the increase in osmolality (Na^+, Cl^-) and the presence of a BBB injury, that no effective transmembrane gradient was established in the injured brain regions sampled.

Colloid oncotic pressure decreased by 49% in association with fluid administration in the normal saline group in our experiment. How does this reduction compare with COP changes that occur in clinical medicine? The literature that examined the clinical effect of COP reduction, principally with a view to its influence on pulmonary gas exchange, indicates that reductions of 35–40% are common.[17–19] For instance, in the investigation by Virgilio *et al.*,[19] the mean reduction in COP in patients in whom normal saline was used to maintain normovolemia during elective abdominal aortic surgery was 40%. Colloid oncotic pressure reductions of 30–35% have been reported in patients resuscitated from hemorrhagic shock.[17] However, in these investigations, the "baseline" COP from which the percentage reduction was calculated was recorded after the onset of shock. These baseline values were less than those seen in healthy, normovolemic persons, suggesting that fluid redistribution had occurred by the time of initial sampling. Accordingly, the severity of COP reduction that occurred in the normal saline group in the present experiment appears likely to occur in patients in the settings of elective surgery and trauma resuscitation.

If changes in the magnitude seen in this investigation occurred in humans, would they be clinically significant? The results of the wet–dry determinations indicated an increase in the percentage of brain water content (saline *vs.* the whole blood or hetastarch groups) of approximately 1%. If the entire brain sustained this increase, it would add approximately 13 ml to the intracranial space of an adult with a brain that weighed 1,300 g. This volume would be tolerated by a healthy person but could well be catastrophic in a patient whose compensation mechanisms are already exhausted.

In conclusion, the present data indicate that, in the context of a mild to moderate parasagittal FPI in rats, reduction of colloid oncotic pressure to approximately 50% of its baseline value without concomitant reduction of osmolality resulted in greater edema accumulation in both gray and white matter than was observed with isovolemic hemodilution with either whole blood or hetastarch. These results lend some support to the clinical concern that reduction of COP *per se* by aggressive administration of isotonic crystalloid has the potential to contribute to the formation of post-traumatic cerebral edema.

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