The Acute Cerebral Effects of Changes in Plasma Osmolality and Oncotic Pressure

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Although it is generally accepted that a decrease in plasma oncotic pressure may result in the formation of peripheral edema, the effect of a hypo-oncotic state on brain water content is less well known. Therefore, utilizing the technique of hollow-fiber plasmapheresis to manipulate plasma composition, the authors examined the effects of acute changes in either plasma osmolality or colloid oncotic pressure on the EEG, regional cerebral blood flow, intracranial pressure, and brain tissue specific gravity (as a measure of cerebral water content) in anesthetized, neurologically normal New Zealand white rabbits. Animals in which either osmolality or oncotic pressure was decreased by plasma replacement with an appropriate solution were compared with a group of control animals in which both of these variables were maintained constant. Animals in which plasma osmolality was decreased by 13 ± 6 mOsm/kg (from a baseline value of 295 ± 5 mOsm/kg) showed evidence of a significant increase in cortical water content (≈0.5%), whereas a 65% reduction in oncotic pressure (from 20 ± 2 mmHg to 7 ± 1 mmHg) failed to produce any change. There were no significant differences in mean arterial pressure, central venous pressure, regional cerebral blood flow, or the EEG between any of the groups. Although intracranial pressure increased in all groups, the largest increase (8.1 ± 4.4 mmHg) occurred in those animals whose osmolality was reduced. The increase in intracranial pressure in animals rendered hypo-oncotic was no different from the "control" group (2.4 ± 0.9 mmHg vs. 3.0 ± 1.5 mmHg). This study suggests that an acute fall in oncotic pressure does not promote an increase in cerebral water content in the non-injured brain. Unlike peripheral tissues, the presence of the blood-brain barrier with its small pore size and limited permeability may serve to enhance the importance of osmolality and minimize the role of oncotic pressure in determining water movement between the vasculature and brain tissue. (Key words: Blood: plasmapheresis. Brain: blood flow; edema; intracranial pressure. Fluid balance: colloid oncotic pressure; colloids; crystalloids; hetastarch; osmolality. Plasma oncotic pressure. Shock, hemorrhagic: resuscitation.)

IT IS GENERALLY BELIEVED that the intravenous administration of large volumes of crystalloid solutions may result in peripheral edema, and that this edema is caused by a decrease in plasma colloid oncotic pressure (COP).[1] Many clinicians also feel that a similar phenomena occurs in the brain during crystalloid resuscitation,

with the resultant production of cerebral edema and the development of intracranial hypertension.[2,3] A recent study examining the cerebral effects of profound hemodilution with lactated Ringers or hetastarch solutions (as a model of massive fluid replacement) tends to support this view.[4] Unfortunately, plasma COP was not measured in this study, and small decreases in plasma osmolality occurred in animals given lactated Ringers. As a result, it was not clear whether the observed increases in intracranial pressure (ICP) and brain water content following crystalloid administration were a result of changes in plasma osmolality or COP. The increase in brain water content following the administration of lactated Ringers may have been due either to its relative hypo-osmolality (273 mOsm/l vs. 310 mOsm/l for 6% hetastarch) or its lack of colloidal properties (COP of 0 mmHg vs. ≈20 mmHg for 6% hetastarch).

To better resolve these questions, we studied the acute cerebral effects of changes in plasma osmolality and COP in anesthetized, neurologically normal New Zealand white rabbits. By employing the technique of plasmapheresis, we were able to selectively alter either plasma osmolality or COP without significant changes in mean arterial pressure, central venous pressure, or hematocrit. Three groups of animals were used. In two of the groups, we selectively decreased either plasma osmolality or COP while holding the other variable constant. In the third group, plasmapheresis was performed without changes in either osmolality or COP. Comparisons made between these three groups allowed us to identify the acute cerebral effects resulting from changes in plasma osmolality or COP.

Materials and Methods

Fifteen New Zealand white rabbits of either sex, weighing 3.4–3.9 kg, were anesthetized with 4% halothane in oxygen. A 22-gauge catheter was inserted into a marginal ear vein and 2 mg of pancuronium administered. The trachea was rapidly intubated under direct vision with a 3-mm ID cuffed endotracheal tube. The cuff was inflated to occlusion and the lungs mechanically ventilated (V_t = 45 ml, rate = 30/min) with 66% nitrous oxide in oxygen and 0.5–0.7% halothane (inspired). CO_2 was added to the gas mixture to achieve a Pa_{CO_2} between 34 and 38 mmHg, and an esophageal temperature probe was inserted to maintain body temperature at 36–38° C through the use of servo-con-

trolled heat lamps. Following infiltration with 0.25% bupivicaine, bilateral groin incisions were made for the placement of catheters into the femoral artery, the right atrium (position confirmed by monitoring of waveform during pullback from the right ventricle), and into the inferior vena cava. The animal was then turned into a prone "sphinx" position and the head fixed in a stereotactic holder with the interaural line approximately 10 cm above the midchest. A second marginal ear vein was then cannulated using a 20-gauge catheter. The scalp was infiltrated with 0.25% bupivicaine, incised in the midline, and reflected laterally to expose the skull. Bilateral burr holes 1 mm in diameter were drilled at points 3 mm lateral to the sagittal and 3 mm posterior to the coronal sutures. Two 150-μm diameter platinum-iridium alloy needle electrodes (Grass® Instrument Co., Model E2, Quincy, MA) were advanced using stereotactic manipulators through the dura and 2–3 mm into the underlying cortex. These electrodes were referenced to a silver wire electrode placed in the subcutaneous tissue of the animals' back and were used for the determination of regional cerebral blood flow (rCBF) by the hydrogen clearance technique (see below).[5,6] Two additional needle electrodes were placed biparietally in the scalp for the continuous recording of the EEG. Finally, a posterior midline neck incision was made and a 21-gauge butterfly needle advanced under direct vision through the atlanto-occipital membrane into the cisterna magna for measurement of ICP. The insertion site was sealed using Eastman 910™ cement.

Arterial and central venous pressure transducers were zeroed at mid-thoracic level. The ICP transducer was zeroed at head level. Continuously monitored variables included mean arterial pressure, central venous pressure, ICP, EEG, and esophageal temperature. rCBF determinations were made upon initiation and immediately prior to conclusion of plasmapheresis using the hydrogen clearance method.[5,6] This technique involves the addition of $\approx 5\%$ hydrogen gas to the inspired mixture until tissue saturation is achieved. The current flow between the platinum and silver electrodes due to the spontaneous oxidation of the hydrogen is proportional to the partial pressure of hydrogen in the tissue surrounding the platinum electrode. When the hydrogen is discontinued, the resulting washout curves can be analyzed using the $T_{1/2}$ method[7] to derive regional blood flow in $ml \cdot 100 \ g^{-1} \cdot min^{-1}$ (note: while two hydrogen electrodes were implanted in each animal, reported values are the average of the two hemispheric flows). Plasma osmolality was determined using a Precision Instruments freezing-point depression osmometer. COP was measured on an Instrumentation for Physiology and Medicine, Inc., oncometer using an Amicon® PM30 membrane.

TABLE 1. Oncotic Pressure and Osmolality of Infused Solutions

	COP (mmHg)	Osmolality (mOsm/kg)
HYPO OSM	20	112
HYPO ONC	0	308
CONTROL	20	308

Following completion of the surgical preparation, the animals were given 2000 u of heparin and 1.5 mg of pancuronium intravenously. Six milliliters of blood was withdrawn from the femoral artery for determination of hematocrit, osmolality, COP, pH, Pa_{CO_2}, and Pa_{O_2}. Each animal was then randomized to one of three experimental groups based upon the type of custom-made replacement fluid it would receive while undergoing plasmapheresis: 1) HYPO OSM animals had their filtered plasma replaced with a dilute solution of lactated Ringers containing 6% hetastarch (this solution was prepared by dissolving 30 g of hetastarch in 400 ml of de-ionized water and 100 ml of lactated Ringers); 2) HYPO ONC animals' plasma was replaced with a modified lactated Ringers solution made by adding 187 mg of sodium chloride to 500 ml of lactated Ringers; and 3) CONTROL animals received a solution of 6% hetastarch in lactated Ringers compounded by adding 30 g of hetastarch to 500 ml of lactated Ringers. The final measured COP and osmolality of these three solutions are shown in table 1.

Following the recording of baseline values for mean arterial pressure, central venous pressure, ICP, and rCBF, plasmapheresis was begun using a polypropylene hollow fiber pheresis filter (CPS-10™, Travenol Laboratories, Deerfield, IL) which had been primed with 60 ml of stored, heparinized (1000 u) rabbit blood.[8,9] Venous blood from the inferior vena cava was pumped into the filter at 10–12 ml/min which produced an inlet pressure of 60–150 mmHg. This resulted in plasma being separated from the cellular components of the blood at a mean rate of 3 ml/min. The cellular elements of the blood (with a hematocrit of approximately 62%) were returned to the animal via the 20-gauge marginal ear vein catheter. The selected replacement fluid (see above) was administered through the 22-gauge ear vein catheter at a rate sufficient to maintain the central venous pressure at its baseline value. If needed, a dilute solution of angiotensin (8 μg/ml) was infused to maintain the mean arterial pressure greater than 70 mmHg (angiotensin was selected as a vasopressor because of its minimal effects on the cerebral vasculature).[10] Following 45 min of plasmapheresis, a second blood sample was obtained, mean arterial pressure, central venous pressure, ICP, and rCBF recorded, and the animals killed by rapid exanguination followed by

TABLE 2. Pre- and Post-pheresis Values for Mean Arterial Pressure (MAP), Central Venous Pressure (CVP), Regional Cerebral Blood Flow (rCBF), and Intracranial Pressure (ICP)

	MAP (mmHg)		CVP (mmHg)		rCBF (ml/100g/m)		ICP (mmHg)		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Change
HYPO OSM	90 ± 9	91 ± 8	2.0 ± 2.0	2.7 ± 1.5	41 ± 6	36 ± 3	0.5 ± 1.3	8.6 ± 4.5	8.1 ± 4.4*
HYPO ONC	88 ± 8	79 ± 7	0.2 ± 1.5	1.6 ± 2.3	39 ± 4	36 ± 9	0.4 ± 0.4	2.8 ± 1.0	2.4 ± 0.9
CONTROL	86 ± 11	86 ± 13	2.8 ± 2.3	2.5 ± 2.0	51 ± 10	36 ± 8	1.1 ± 1.7	4.1 ± 0.8	3.0 ± 1.5

All values are mean ± SD. rCBF values represent the mean of right and left hemispheric flow determinations.

* $P < 0.05$ vs. HYPO ONC group, $P \approx 0.06$ vs. CONTROL group following Bonferroni corrections for multiple comparisons.

an intravenous bolus of potassium chloride. The brains were rapidly removed and placed in cold (4° C) kerosene for 15 min. Small samples (volume ≈ 2 mm^3) of parietal cortex and underlying white matter were dissected free and placed in a linear kerosene/bromobenzene density gradient for determination of the specific gravities.[11,12] The gradient was calibrated following each set of determinations using K_2SO_4 standards.[13]

Data for the three groups were compared using a one-way analysis of variance and, when indicated, t tests with Bonferroni corrections. Significance was assumed for P values <0.05 (after correction for multiple comparisons).

Results

There were no intergroup differences in baseline values prior to plasmapheresis for mean arterial pressure, central venous pressure, ICP, rCBF (table 2), hematocrit, pH, Pa_{O_2}, Pa_{CO_2}, osmolality, or COP. Following the plasmapheresis, no intergroup differences existed for mean arterial pressure, central venous pressure, rCBF, hematocrit, pH, Pa_{O_2}, Pa_{CO_2}, angiotensin dose, or the volume of plasma removed (tables 2, 3). Inspection of the EEGs revealed no differences between the various groups during the course of the experiment. Animals in the CONTROL group required significantly less replacement fluid (150 ± 25 ml) than either HYPO OSM (205 ± 20 ml) or HYPO ONC (221 ± 47 ml) animals in order to maintain a stable central venous pressure. As intended, osmolality decreased in the HYPO OSM group (Δosmolality $= -13 \pm 6$ mOsm/kg)

with an unchanged COP. Conversely, COP decreased in the HYPO ONC group (ΔCOP $= -12.5 \pm 3$ mmHg) in the presence of a stable plasma osmolality.

ICP rose in all groups with the greatest increase seen in HYPO OSM rabbits (Δ ICP $= 8.1 \pm 4.4$ mmHg, $P < 0.05$ vs. HYPO ONC group) (table 2). Furthermore, cortical specific gravity was significantly reduced ($P < 0.01$) only in the HYPO OSM group. (Note: Since the specific gravity of water is 1.0000, a *decrease* in specific gravity indicates an *increase* in water content.) In spite of a significant decrease in COP in the HYPO ONC group, there were no differences in specific gravity between the HYPO ONC and CONTROL groups (fig. 1).

Discussion

This study examined the acute cerebral effects of relatively rapid changes in plasma osmolality and oncotic pressure. It was performed upon normal animals to minimize the number of potentially confusing variables which would have been introduced had we utilized a model of cerebral injury. We felt it important to define the effects of changes in COP and osmolality in animals with an intact blood-brain barrier before moving to the more complex (although more relevant) situation where some form of neurologic injury has occurred.

A number of the methods used in this experiment deserve some discussion. First, the technique of hollow-fiber plasmapheresis was chosen for this investigation as it allowed the rapid alteration of plasma composition with minimal changes in mean arterial pressure, central venous pressure, or hematocrit. The device employed is

TABLE 3. Post-pheresis Values (Mean ± SD)

	Plasma Removed ml	Fluid in ml	pH	Pa_{CO_2} mmHg	Pa_{O_2} mmHg	HCT %	OSM mOsm/kg	ONC mmHg
HYPO OSM	130 ± 14	205 ± 20	7.42 ± .06	34 ± 2	183 ± 5	34 ± 1	282 ± 5†	22 ± 3
HYPO ONC	116 ± 27	221 ± 47	7.32 ± .07	35 ± 3	191 ± 22	39 ± 5	303 ± 11	7 ± 1‡
CONTROL	130 ± 13	150 ± 25*	7.39 ± .04	35 ± 1	177 ± 10	35 ± 5	298 ± 3	19 ± 1

* $P < 0.05$, †$P < 0.01$, ‡$P < 0.001$ vs. all other groups.

a commercially available hollow-fiber filter with a maximum pore size of 0.55 μm and a total surface area of 0.17 square meters (Travenol Laboratories, product information on the CPS 10™ Capillary Membrane Separator). As blood is pumped into the fibers, hydraulic pressure forces plasma through the pores, while the cellular elements of the blood are retained and returned to the animal. These filters allow the free passage of most plasma constituents, including albumin, fibrinogen, total protein, and IgG.[8,9] As a consequence, plasma composition can be easily altered by the concurrent administration of an appropriate replacement solution. We selected hetastarch as the colloid replacement compound because of its growing clinical popularity, its cost, and because of previous difficulties (allergic?) encountered in our laboratory when giving large volumes of commercial human albumin to rabbits.

Second, the rCBF values need to be interpreted with caution. The hydrogen clearance method is well established and in widespread use.[5,6] However, the platinum electrodes measure blood flow in a tissue volume with a radius of approximately 2–3 mm.[14,15] Since the rabbit cortex is only 3–3.5 mm in depth, the values reported here are a weighted average of white and grey matter flows. While comparisons between flow measurements of the various groups are valid, the absolute flow rates may not be comparable with those derived by other methods.

Lastly, some mention needs to be made of the use of microgravimetry to detect changes in brain water content. The validity of this method has been repeatedly confirmed,[11,12,13] and its sensitivity is again demonstrated in this experiment, as we were able to show a decrease in cortical specific gravity associated with a relatively small drop in plasma osmolality (13 ± 6 mOsm/kg). Although the method is relatively insensitive to variation in the amount of blood remaining in the post mortem brain,[16] we exanguinated all animals to further minimize this potential source of error.[11] Specific gravities can be reported as the more familiar per cent water content. However, this conversion requires making certain assumptions about the composition of the interstitial fluid. As we were primarily interested in this study with *changes* in water content, rather than its absolute value, we chose to report the numbers as observed. However, as a point of reference, a normal grey matter specific gravity of 1.0430 (CONTROL, grey) corresponds to approximately 81.16% water, while a specific gravity of 1.0417 (HYPO OSM, grey) indicates a water content of about 81.75%.§

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§ Conversion performed using the equations of Nelson *et al.*,[11] using data obtained in the rabbit by C. Tommasino, M. D., personal communication.
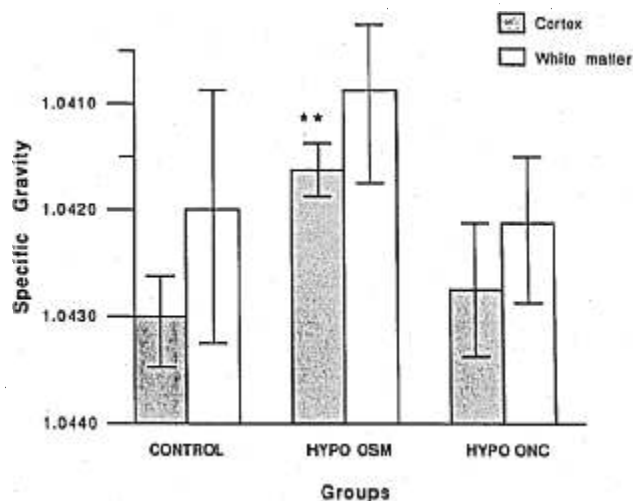

FIG. 1. Cortical and white matter specific gravities of the three groups upon completion of the plasmapheresis. Note: The greater the specific gravity, the lower the water content (*i.e.*, brain tissue with a specific gravity of 1.0430 contains less water than tissue with a specific gravity of 1.0417). **$P < 0.01$ *vs.* other groups.

The Starling equation is a mathematical attempt to define the forces which control the movement of water between blood and the interstitial fluid space. In most textbooks, this equation is presented in a fashion which describes the hydrostatic forces acting to drive fluid out of the vascular space (high intra-capillary pressure *vs.* a low interstitial pressure) being balanced by an oncotic gradient which acts to draw fluid back into the capillary (high intravascular protein concentration *vs.* a low interstitial concentration).[17,18] The result of these opposing forces is either no net fluid movement, or, more commonly, a slight outward movement with interstitial accumulation being prevented through drainage by the lymphatics. Using this model, one would predict that a profound reduction in intravascular oncotic pressure would result in an increase in fluid efflux from the capillaries and, perhaps, an increase in interstitial edema. This is the most commonly given explanation for the severe peripheral edema which occasionally develops in patients resuscitated with large volumes of crystalloids.

The results of the current experiment would appear to contradict this prediction. In the HYPO ONC animals, a 65% reduction in COP (from 20 mmHg to 7 mmHg) was not associated with any changes in brain specific gravity (no increase in water content). This final COP value is, in fact, *lower* than typically seen in most "resuscitation" situations.[19,20] However, we do not believe that any contradiction exists. Instead, our results point out a factor in the Starling equation which is often forgotten. The ability of a solute to produce a fluid flux across a membrane depends on the molecular weight

(size) of the solute and the pore size or permeability of the membrane separating the two compartments. In peripheral tissues, capillaries tend to be "leaky" with a pore size of approximately 65 Å.[21] As a consequense, ionic solutes (sodium, potassium, chloride) freely equilibrate between the intravascular and interstitial compartments, whereas high molecular weight compounds (albumin, immunoglobulins, hetastarch) are retained intravascularly, and are able to produce a gradient favoring the movement of water from the interstitium into the capillaries. The brain, by contrast, is unique in that it is isolated from the vasculature by the blood-brain barrier which has an estimated pore size of only 8 Å.[21] This small pore size and resultant limited permeability enhances the importance of ionic solutes in determining water movement between the interstitium and the vasculature. If the presence of the blood-brain barrier causes the brain to act more like an osmometer, rather than an oncometer, small changes in plasma osmolality would be expected to produce very large pressure gradients for water flux across the blood-brain barrier, dwarfing the importance of alterations in COP.[22] For an ideal osmometer, it has been calculated that a gradient of 1 mOsm/l across the membrane would produce a hydrostatic gradient of 19.3 mmHg,[23] which is approximately equal to the total COP of plasma.

Many other factors may also play a role in limiting the production of cerebral edema secondary to a fall in COP. Unlike peripheral tissues, the cerebral cortex is made up of a tightly interwoven, non-compliant matrix of neurons, glial cells, and unmyelinated fibrils. Due to the relative inelasticity[24] of this tissue, a small increase in interstitial water content may result in a large increase in interstitial hydrostatic pressure which would oppose the further flux of water into the tissue. To produce a significant increase in the interstitial water content of the cortex may require a hydrostatic gradient greater than that which can be produced by even a dramatic decrease in COP.

In summary, this study shows that, in non-lesioned brains, a 65% reduction in plasma COP fails to have any acute effect on cortical water content, whereas only a 4% decrease (13 mOsm/kg) in plasma osmolality leads to a significant increase as assayed by a microgravimetric technique. White matter water content showed a similar pattern, although the differences were not statistically significant due to large standard deviations (possibly due to the difficulty in isolating homogenous samples of white matter from the rabbit brain). These results suggest that, in the non-lesioned brain with an intact blood-brain barrier, plasma osmolality, rather than COP, is the primary determinant of net water flux

between the vasculature and brain parenchyma. What may occur in the case of cerebral injury is difficult to predict. Depending on the degree of damage sustained by the blood-brain barrier, COP may or may not become an important factor in the production of cerebral edema. Further experiments will be required to help resolve this important question.

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