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Differential Effect of Oncotic Pressure on Cerebral and Extracerebral Water Content during Cardiopulmonary Bypass in Rabbits

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To study the effect of oncotic pressure on brain water content during cardiopulmonary bypass (CPB), 14 anesthetized New Zealand White rabbits underwent 60 min of nonpulsatile CPB at normothermia. Animals were grouped according to the composition of the circuit priming fluid. Group 1 animals (n = 7) received a priming fluid (6.5% hydroxyethyl starch in 0.72 N NaCl; 323 ± 13 mOsm/kg [mean ± SD]) that maintained normal colloid oncotic pressure (COP) during CPB (19.0 ± 1.5 mmHg). Group 2 animals (n = 7) received a priming fluid (0.9 N NaCl; 324 ± 23 mOsm/kg) that led to a hypooncotic state (COP = 6.2 ± 1.2 mmHg). Blood chemistries and hemodynamics were recorded every 15 min during CPB. Animals were given additional priming fluid and sodium bicarbonate during CPB to maintain a circuit flow of 85 ml·kg^{-1}·min^{-1} and arterial *p*H greater than 7.35. There were no significant differences between groups 1 and 2 with respect to temperature, central venous pressure, mean arterial pressure, Pa_{O_2}, Pa_{CO_2}, plasma sodium concentration, or osmolality at any time during CPB, although osmolality increased in both groups. After 60 min of bypass, animals were killed and organ water contents were determined by wet/dry weight ratios. A separate group of nine similarly prepared and anesthetized animals that did not undergo cannulation or CPB also underwent measurement of plasma chemistries and tissue water contents and served as nonbypass controls (group 3). Brain and kidney water contents were unaffected by oncotic pressure, whereas duodenum and skeletal muscle had significantly greater water content (*P* = 0.003 and *P* = 0.008, respectively) after hypooncotic CPB. To maintain flow and *p*H, group 2 (hypooncotic) animals required an average of 313 ± 82 ml additional fluid and 14 ± 7 mEq bicarbonate, whereas group 1 (isooncotic) animals required only 21 ± 27 ml additional fluid (*P* = 0.0001) and 3 ± 4 mEq bicarbonate (*P* = 0.0025). All tissue water contents were identical between the control (group 3) and group 1 animals. These results indicate that the mechanisms that maintain brain fluid balance remain intact during nonpulsatile hypooncotic CPB. Fluid and bicarbonate requirements, and edema formation in other tissue beds can be minimized by maintenance of normal oncotic pressure during CPB. (Key words: Brain: edema. Cardiopulmonary bypass; complications. Fluids: colloid oncotic pressure; osmolality.)

SEVERAL STUDIES HAVE SHOWN that total body interstitial water is increased 15–30% for 24–48 h following cardiopulmonary bypass (CPB), whereas intracellular water content is unchanged.[1–3] Whether particular vital organs are more or less susceptible to interstitial fluid accumulation (edema formation) during bypass has received little attention, although the lung[4] and heart[5] have been the organs of greatest interest. The effects of CPB upon central nervous system (CNS) volume regulation and brain water content have not been studied extensively.

Cardiopulmonary bypass differs from normal circulation in several ways that may predispose to tissue edema. Hemodilution during CPB, usually achieved with hypooncotic priming solutions, decreases colloid oncotic pressure (COP) at least 25–50%.[2,4,6,7] This should theoretically result in increased fluid transfer into the interstitial space. Some data also suggest capillary permeability is increased during CPB.[8] If so, interstitial edema might occur during CPB even if hydrostatic and oncotic forces are maintained at normal values. Finally, early animal studies indicate that nonpulsatile flow impairs lymphatic function.[9] If so, decreased lymphatic clearance of interstitial water would augment the accumulation of edema fluid regardless of the mechanism of formation. Because cerebral edema may compromise cerebral blood flow, particularly in regions of cerebral ischemia or infarction,[10,11] these characteristics of CPB may contribute to the appearance of neurologic deficits following cardiac surgery.

With these considerations in mind, we posed the following questions regarding CNS volume regulation during CPB: 1) Does nonpulsatile CPB result in brain water

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accumulation when hydrostatic, osmotic, and oncotic forces are maintained at approximately normal nonbypass values? and 2) Does nonpulsatile CPB predispose the brain to fluid accumulation in hypooncotic states?

Materials and Methods

Basic Preparation

The experimental protocol was approved by the Animal Care Committee of the University of Iowa School of Medicine. Anesthesia was induced with 5% halothane in O_2 in 14 New Zealand White rabbits (weight, 4.5 ± 0.5 kg [mean ± SD]) in a plastic box. After cannulation of a marginal ear vein and tracheal intubation with a 3.0-mm ID cuffed tube (Mallinckrodt, Glens Falls, NY), the animals were paralyzed with 1 mg/kg succinylcholine and their lungs ventilated to achieve normocarbia (guided initially by capnography and later by arterial blood gas analysis) using a gas mixture containing 1.5% halothane in 33% O_2/balance N_2O. Paralysis was maintained with succinylcholine added to a maintenance lactated Ringer's solution (4 $ml \cdot kg^{-1} \cdot h^{-1}$) in amounts sufficient to ensure delivery of 3 $mg \cdot kg^{-1} \cdot h^{-1}$. Esophageal temperature was kept at 37–39° C with a servocontrolled heating pad. *Via* a groin incision, catheters were inserted into the abdominal aorta and inferior vena cava to allow continuous monitoring of arterial and central venous pressures and intermittent blood sampling. A 3-ml arterial sample was then obtained for measurement of baseline blood gases, *p*H, hematocrit, plasma Na^+ concentration (in duplicate *via* flame photometry), osmolality (freezing point depression, Osmette A®, Precision Systems Inc., Sudbury, MA), and oncotic pressure (Wescor 4400, SS-30 membrane, Logan, UT).

Sternotomy and Cannulation

After initial preparation, a median sternotomy was performed, and the thymus and pericardium were reflected. Halothane, N_2O, and maintenance fluids were then discontinued, and each animal received a loading dose of fentanyl and diazepam, followed by a continuous infusion of each for the remainder of the experiment (fentanyl: 100 $\mu g/kg$ loading dose, 2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion; diazepam: 2 mg/kg loading dose, 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion). Pancuronium (0.1 mg/kg) was used for subsequent muscle relaxation. The animal's blood was anticoagulated with 300 U/kg of heparin, achieving an activated clotting time greater than 900 s. An 18-French venous catheter (Polystan, Ballerup, Denmark) was placed through a purse-string suture in the right atrium, and a 10 cm long 10-G catheter (Deseret, Sandy, UT) was similarly placed in the ascending aorta (distal orifice ≈3 mm above the aortic valve) *via* the left ventricular apex. Subsequent studies using radioactive microspheres have shown equal hemispheric perfusion with this system.

Cardiopulmonary Bypass

The CPB circuit consisted of a model 540® centrifugal blood pump with a BP-50® pump head (Biomedicus, Eden Prairie, MN), a Capiox II 08® membrane oxygenator/heat exchanger (Terumo Corporation, Piscataway, NJ), and a heater/cooler (VWR Scientific, San Francisco, CA). Priming volume of the circuit was approximately 200 ml. (See below for details regarding priming fluids.)

Cardiopulmonary bypass was initiated at a flow rate of 85 $ml \cdot kg^{-1} \cdot min^{-1}$ (reported previously to provide adequate tissue oxygen delivery in rabbits undergoing CPB[12]) and monitored with a calibrated in-line electromagnetic flow meter (Biomedicus® TX40P). The oxygenator was ventilated with a variable mixture of oxygen and nitrogen to achieve Pa_{O_2} of near 250 mmHg and Pa_{CO_2} near 40 mmHg. Because this perfusion system lacks an in-circuit venous reservoir, the animal acted as its own venous reservoir. When venous return decreased, the negative pressure created by the centrifugal pump caused the atrial walls to collapse upon the venous cannula, creating an intermittent, "staccato" venous return that limited bypass flow.[13] In each experimental group, the appearance of this sign was used as the indication for administration of additional priming fluid to maintain the desired flow rate of 85 $ml \cdot kg^{-1} \cdot min^{-1}$. At 15-min intervals, 3 ml arterial blood was withdrawn from the animal for measurement of blood gases, *p*H, hematocrit, plasma Na^+ concentration, and osmotic and oncotic pressure. Sodium bicarbonate was administered to maintain *p*H > 7.35.

Bypass Fluid Groups

Bypass animals were assigned to one of two groups based on the composition of the pump priming fluid. In group 1 animals (n = 7), the priming fluid consisted of 350 ml 6.5% hydroxyethyl starch (E. I. DuPont, Bannockburn IL) in 0.72 N sodium chloride to which was added 250 mg $CaCl_2$ and 1000 U heparin. In addition, 100–150 ml of filtered fresh-packed donor rabbit red blood cells (collected in citrate/phosphate/dextrose) were added, depending upon the volume available from the donor rabbit. In group 2 animals (n = 7), the priming fluid consisted of 350 ml 0.9 N sodium chloride with additional $CaCl_2$, heparin, and rabbit red blood cells as per group 1. Prime *p*H was adjusted to approximately 7.4 with sodium bicarbonate, and the prime composition was measured (hematocrit, sodium, osmolality, and oncotic pressure) before bypass (table 1). Priming fluid in excess of that required for circuit priming was used for supple-

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TABLE 1. Priming Fluid Composition

Variable	Group 1 Hydroxyethylstarch (n = 7)	Group 2 Saline (n = 7)
Oncotic pressure (mmHg)	20.7 ± 0.9	0.2 ± 0.2†
Osmolality (mOsm/kg)	323 ± 13	324 ± 23
Sodium* (mmol/l)	137 ± 7	160 ± 4‡
Hematocrit (%)	11 ± 2	12 ± 3
*p*H	7.32 ± 0.11	7.35 ± 0.04

Mean ± SD.
* n = 4 for group 1; n = 6 for group 2. Samples not included had been accidently discarded prior to analysis.
† Significantly different from Group 1, $P = 0.0001$.
‡ Significantly different from Group 1, $P = 0.0007$.

mental fluid administration during CPB as described above.

TISSUE WATER CONTENT

After 60 min of bypass, the animals were killed by discontinuation of CPB and intracardiac administration of saturated KCl solution. One- to 2-g portions of the following structures were rapidly dissected and placed in dry, preweighed vials to determine wet weight: right and left cerebral hemispheres, cervical spinal cord, kidney, skeletal muscle (masseter), and duodenum. Tissue samples were then dried at 80° C over 3–5 days to constant weight. Organ water content (per cent) was calculated as the difference between wet and dry weights divided by wet weight.

NONBYPASS CONTROLS (GROUP 3)

To permit evaluation of the effects of CPB *per se*, plasma chemistries and tissue water contents were also measured in a group of nine rabbits studied in a separate protocol that did not involve either cardiac cannulation or CPB. Because the basic preparation, anesthetic and hemodynamic profile, and total experimental duration of 3–4 hours was equivalent to bypass animals, we have included their time-related results as nonbypass controls.

STATISTICS

Tissue water content in the three groups was examined using a one-way analysis of variance (ANOVA). Hemodynamic and blood data were examined by two-way ANOVA (bypass group, time on CPB), with time on CPB treated as the repeated variable. Significance was assumed for $P < 0.05$. All results are expressed as mean ± SD.

Results

Physiologic data from the bypass animals are shown in table 2. There were no significant differences between groups 1 and 2 with respect to temperature (38.2 ± 1.3 *vs.* 37.0 ± 1.0° C), central venous pressure (4 ± 3 *vs.* 5

TABLE 2. Blood and Hemodynamic Data of Groups 1 and 2 before and at Intervals during Cardiopulmonary Bypass

Variable	Group	Baseline	Duration of CPB (min) 15	30	45	60
Oncotic pressure (mmHg)	1 (n = 7)	18.7 ± 1.3	18.8 ± 1.6	19.2 ± 1.5	18.9 ± 1.7	18.9 ± 1.6
	2 (n = 7)	19.2 ± 1.5	6.1 ± 1.2	6.3 ± 1.1	6.4 ± 1.2	6.2 ± 1.4
Osmolality* (mOsm/kg)	1	304 ± 6	321 ± 10	327 ± 11	330 ± 11	335 ± 8
	2	311 ± 12	330 ± 11	334 ± 13	336 ± 11	336 ± 14
Sodium (mmol/l)**	1	138 ± 7	137 ± 6	137 ± 6	137 ± 7	137 ± 7
	2	136 ± 7	142 ± 7	140 ± 6	138 ± 6	144 ± 6
Hematocrit† (%)	1	41 ± 6	23 ± 2	21 ± 2	21 ± 2	21 ± 2
	2	43 ± 6	29 ± 3	28 ± 5	29 ± 4	27 ± 4
*p*H‡	1	7.44 ± .04	7.45 ± .06	7.39 ± .02	7.33 ± .05	7.32 ± .08
	2	7.45 ± .02	7.34 ± .07	7.32 ± .04	7.32 ± .05	7.34 ± .04
Mean arterial pressure (mmHg)	1	83 ± 18	67 ± 13	70 ± 12	71 ± 10	68 ± 10
	2	84 ± 19	60 ± 15	60 ± 13	63 ± 13	64 ± 12
Pump flow ($ml \cdot kg^{-1} \cdot min^{-1}$)	1	—	88 ± 3	87 ± 5	90 ± 4	90 ± 3
	2		86 ± 4	86 ± 4	87 ± 4	91 ± 5
Fluid required (ml)	1	—	—	—	—	21 ± 27
	2	—	—	—	—	313 ± 82§
Bicarbonate required (mEq)	1	—	—	—	—	3 ± 4
	2	—	—	—	—	14 ± 7¶

Mean ± SD.
CPB = cardiopulmonary bypass.
* Osmolality increased significantly in both groups during CPB, $P = 0.008$.
† Groups 1 and 2 significantly different during CPB, $P = 0.01$.
‡ Group 2 significantly more acidotic than group 1 during CPB, $P = 0.05$
§ Significantly different from group 1, $P = 0.0001$.
¶ Significantly different from group 1, $P = 0.0025$.
** n = 4 group 1, n = 6 group 2. Samples not included had been accidentally discarded prior to analysis.

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± 2 mmHg), Pa_{O_2} (297 ± 127 *vs.* 256 ± 155 mmHg), or Pa_{CO_2} (36 ± 6 *vs.* 40 ± 7 mmHg) during CPB, respectively. Total flow was maintained at approximately 88 $ml \cdot kg^{-1} \cdot min^{-1}$ and arterial *p*H at 7.35 for 60 min in each bypass group, although group 2 animals tended to be more acidotic during the early phase of CPB ($P = 0.05$). Group 2 (hypooncotic) animals had numerically lower average mean arterial pressures at equivalent bypass flow rates than group 1 (isooncotic) animals, but group means were not significantly different. To maintain flow and *p*H, group 2 animals required an average of 313 ± 82 ml additional fluid and 14 ± 7 mEq bicarbonate. In contrast, group 1 animals required only 21 ± 27 ml additional fluid ($P = 0.0001$) and 3 ± 4 mEq bicarbonate ($P = 0.0025$). Despite equivalent values for baseline (pre-CPB) and priming hematocrit, and much greater volume requirements, hypooncotic group 2 animals had significantly higher hematocrits during CPB than isooncotic group 1 animals ($P = 0.01$).

Oncotic pressure was stable during CPB, averaging 19.0 ± 1.5 mmHg in group 1 animals and 6.2 ± 1.2 mmHg in group 2 ($P = 0.0001$). Osmolality was greater during CPB in groups 1 and 2 compared to prebypass baseline and increased over time ($P = 0.008$). However, there was no significant difference in osmolality or plasma sodium concentration between groups 1 and 2 at any time. Control animals (group 3) had an average oncotic pressure of 18.8 ± 1.5 mmHg, with osmolality increasing from 304 ± 10 to 318 ± 13 mOsm/kg over the 3-h fentanyl/diazepam infusion period ($P = 0.025$, paired *t* test).

Despite the marked differences in volume requirement and hematocrit, there were no significant differences in brain, spinal cord, or kidney water content among the three groups. In contrast, tissue water content was significantly greater in skeletal muscle (masseter; $P = 0.008$) and duodenum ($P = 0.003$) after 60 min of CPB in hypooncotic animals (group 2) when compared to isooncotic bypass and nonbypass control groups (table 3). There were no differences in tissue water content in any organ between the isooncotic bypass group (group 1) and nonbypass controls (group 3).

Discussion

The few studies examining brain edema following bypass have yielded conflicting results. In 1958, Halley and co-workers measured brain volume using a volumetric displacement technique in dogs after CPB.[14] Thirteen of 27 dogs were found to have increased brain volume. Unfortunately, measurement of brain volume is not an accurate indicator of water accumulation because swelling may occur simply with vascular congestion and enlargement of the intravascular compartment. Obstruction of cerebral venous return can produce such a situation; in fact, caval obstruction from the venous cannula was noted in 31% of the affected animals. In contrast, Utley, using wet/dry weight ratios, found no increase in brain water content following CPB in either hemodiluted or nonhemodiluted animals.[15] Unfortunately, in neither study were hemodynamic, osmotic, or oncotic parameters quantified. Thus, the current report appears to be the first to examine the acute effect of nonpulsatile CPB and altered oncotic pressure on brain water content. Our results clearly show brain water content was not different from nonbypass controls following 60 min of CPB, *irrespective of COP.* In contrast, other tissue beds (skeletal muscle and duodenum) had significantly greater water contents following hypooncotic CPB.

We believe these findings are consistent with other experimental data and with known differences in structure between brain and peripheral capillaries. In the brain, endothelial tight junctions render the capillary bed remarkably impermeable to both ions and large molecules (colloids), although not to water or to lipid-soluble substances. Net water movement is largely dependent on changes in total osmotic pressure.[16] Because colloid osmotic pressure contributes, at most, the equivalent of 0.5–1 mOsm/kg to total osmolality,[16] even large changes in COP have a negligible effect on total osmolality. Thus, blood–brain osmotic gradients, rather than oncotic gradients, determine net water movement.[16–18] Peripheral capillaries differ from those in the brain in that they *are* permeable to ions but remain relatively impermeable to

TABLE 3. Tissue Water Content after 60 minutes of Cardiopulmonary Bypass

Group	Tissue Water Content (%)					
	Right Hemisphere	Left Hemisphere	Spinal Cord	Kidney	Duodenum	Skeletal Muscle
1 (n = 7)	78.4 ± 0.5	78.5 ± 0.4	67.9 ± 1.3	80.6 ± 0.6	76.5 ± 3.4	74.9 ± 1.4
2 (n = 7)	78.6 ± 0.4	78.5 ± 0.8	68.6 ± 0.9	80.6 ± 2.0	82.3 ± 3.3*	77.6 ± 1.2†
3 (n = 9)	78.4 ± 0.6	78.4 ± 0.6	68.0 ± 0.5	80.9 ± 1.9	75.5 ± 3.7	75.4 ± 1.8

Mean ± SD.

Group 2 significantly different than groups 1 and 3 (one-way ANOVA): * $P = 0.003$; † $P = 0.008$.

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oncotically active molecules. Under these circumstances, intravascular-extravascular/interstitial osmotic gradients are difficult to establish and maintain. As a consequence, oncotic and hydrostatic gradients become important determinants of water movement, as described by the Starling equation. One would therefore predict that changes in oncotic pressure might have a major influence on the formation of edema in peripheral tissue but not in the brain. Recently, using nonbypass models, Zornow *et al.*[18] and Kaieda *et al.*[19] found brain water content to be unaffected by changes in plasma oncotic pressure in both normal rabbits and those subjected to cryogenic brain injury. Our data indicate nonpulsatile CPB does not alter these relationships.

In this experiment, as in others,[15,19,20] skeletal muscle and the gastrointestinal tract (small bowel) appeared to be quite susceptible to edema formation in hypooncotic states. Oncotic pressure also influenced bicarbonate and fluid requirements during CPB, with hypooncotic animals requiring nearly 15 times the volume of fluid to maintain bypass flow and five times the amount of bicarbonate to maintain arterial *p*H. Despite these greater volume requirements, hypooncotic animals still had significantly greater hematocrits during bypass than did isooncotic animals. These findings are consistent with a marked translocation of fluid from the intravascular space, impaired tissue perfusion, and possibly, increased metabolic acid (lactic) production in hypooncotic animals. Our finding of unaltered tissue water content following isooncotic CPB suggests either: 1) nonpulsatile CPB does not result in measurable alteration of capillary permeability; or 2) lymphatic function was not significantly impaired and was therefore able to compensate for any increase in transcapillary fluid movement into the interstitium. This latter hypothesis is supported by findings of increased lymphatic flow during CPB in animals in both iso- and hypooncotic states.[8,21]

Although oncotic pressure remained stable during CPB, our unexpected finding was that osmolality increased during CPB in both groups by 25–30 mOsm/kg. Group 2 animals required, on average, 11 mEq more bicarbonate than those in group I, which might be expected to create an osmolar load (22 mOsm), leading to "dehydration" of the brain. During CPB, the volume of extravascular fluid is increased by the volume of the CPB circuit, approximately 200 ml. If extracellular volume is 25–30% of body weight, this indicates the total volume of extracellular fluid during bypass was $0.3 \times 4{,}500 + 0.200 = 1.5$ l. The additional bicarbonate given to group 2 animals in this volume would be expected to increase plasma sodium by $\approx$ 8 mmol/l, which was the observed increase, and intravascular osmolality by $\approx$15 mOsm/kg, which is less than the observed increase. Consequently, the increase in osmolality during CPB cannot be completely ascribed to increased plasma sodium concentration. Glucose and lactate concentrations were not measured, but studies performed recently with this preparation revealed lactate accumulation (5–10 mmol/l) and hyperglycemia (7–14 mmol/l) during 60 min of CPB. Such increases may partially explain the increase in osmolality observed during CPB. Thus, as shown in Table 2, despite differences in bicarbonate requirement, there was no significant difference in plasma osmolality or sodium concentration at any time point between groups 1 and 2. Therefore, the absence of a difference in brain water content in the presence of low oncotic pressure cannot be ascribed to differences in osmolality.

Osmolality also increased significantly in nonbypass group 3 animals, and although well matched to group 1 with respect to oncotic pressure, there was a significant difference in the final value of measured osmolality (335 $\pm$ 8 *vs.* 318 $\pm$ 13 mOsm/kg; $P = 0.01$). Thus, it is at first surprising that there was no difference in brain water content between these groups when brain water content is so highly dependent on osmotic gradients.[16–18] However, for a substance to be osmotically active, a concentration gradient must exist across an impermeable barrier. Osmolality, measured *via* freezing point depression, depends upon the total number of solute molecules, regardless of their permeability characteristics. Because brain water content was equivalent in all groups, it would appear the observed increase in osmolality in both bypass and nonbypass animals was at least partially due to substance(s) that rapidly equilibrate across the blood–brain barrier (possibly propylene glycol,[16] the primary vehicle of the diazepam formulation used in these experiments, or glucose) such that osmotic gradients were not established.

We chose to study rabbits undergoing CPB for several reasons. First, rabbits are of sufficient size that a commercially available pediatric perfusion apparatus can be employed. Second, unlike dogs and cats, which possess rete mirabilae resulting in extensive collateralization between internal and external carotid systems, the rabbit brain is supplied exclusively by the internal carotid and vertebral arteries in a pattern similar to humans.[22] Although subhuman primates have comparable cerebrovascular anatomy, the low cost and ease of care of rabbits compared to primates make them an attractive experimental animal. Third, reproducible models of focal cerebral infarction, both microscopic (embolic)[23,24] and macroscopic (vessel occlusion),[25,26] have been developed for the rabbit such that future studies concerning the effect of CPB on outcome from neurologic injury should be possible. Fourth, the cerebrovascular responses to changes in Pa_{CO_2}[27,28] and arterial pressure[29] are well

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characterized in the rabbit and are virtually identical to human values. Resting cerebral blood flow[25,27] and cerebral metabolic rate for oxygen[28,30] also approximate human values.

The anesthetic chosen was based on the desire to approximate anesthetics used clinically for patients undergoing CPB. Based on clinical,[31-33] electroencephalographic,[34,35] pharmacokinetic,[36,37] and pharmacodynamic[38,††] data for fentanyl and diazepam in the rabbit, we devised a constant infusion technique that would be anticipated to maintain plasma concentrations of at least two times the ED_{95} concentration of each agent. Studies in unparalyzed animals in our laboratory have shown that this regimen completely eliminated all somatic and hemodynamic responses to clamping of the hindpaw web space over a 3-h period without evidence of acute tolerance or tachyphylaxis.

In summary, in rabbits undergoing nonpulsatile CPB, we found that brain water content was unaffected by marked reductions in oncotic pressure produced by a crystalloid priming solution. Hypooncotic animals had exaggerated fluid and bicarbonate requirements during CPB and significant increases in muscle and duodenal water contents as compared to isooncotic animals. Nonpulsatile CPB *per se,* irrespective of oncotic pressure, did not appear to result in brain edema, nor edema in other organs, when oncotic pressure was maintained at normal levels.

†† Bergman SA, Wynn RL, Williams G: Diazepam enhances fentanyl and diminishes meperidine antinociception. Anesth Prog 35: 190–194, 1988.

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