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Regional Cerebral Blood Flow Following Resuscitation from Hemorrhagic Shock with Hypertonic Saline

Influence of a Subdural Mass

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After severe hemorrhage, hypertonic saline restores systemic hemodynamics and decreases intracranial pressure (ICP), but its effects on regional cerebral blood flow (rCBF) when used for resuscitation of experimental animals with combined shock and intracranial hypertension have not been reported. We compared rCBF changes (by radiolabeled microsphere technique) after resuscitation from hemorrhage with either 0.8 or 7.2% saline in animals with and without a right hemispheric subdural mass. We studied 24 mongrel dogs anesthetized with 0.5% halothane and 60% nitrous oxide. In group 1 (n = 12), hemorrhage reduced mean arterial pressure (MAP) to 45 mmHg for 30 min. In group 2 (n = 12), ICP was increased and maintained constant at 15 mmHg, whereas hemorrhage reduced MAP to 55 mmHg for 30 min (cerebral perfusion pressure [CPP] ≈ 40 mmHg in each group). After the 30-min shock period, 6 animals in each group received one of two randomly assigned resuscitation fluids over a 5-min interval: 1) 7.2% hypertonic saline (HS; sodium 1,232 mEq·l^{-1}, volume 6.0 ml·kg^{-1}); or 2) 0.8% isotonic saline (SAL; sodium 137 mEq·l^{-1}, volume 54 ml·kg^{-1}). Once fluid resuscitation began, ICP was permitted to vary independently in both groups. Data were collected at baseline (before subdural balloon inflation in group 2), midway through the shock interval (T15), immediately after fluid infusion (T35), and 60 and 90 min later (T95, T155). In groups 1 and 2, ICP was significantly less in animals resuscitated with HS compared to those receiving SAL ($P < 0.05$). In group 2, rCBF in the right hemisphere was significantly greater in HS-treated than in SAL-treated dogs ($P < 0.05$). We conclude that when used for resuscitation from hemorrhagic shock with associated intracranial hypertension, 7.2% HS reduces ICP and increases rCBF. (Key words: Hypertonic saline. Brain, subdural mass: cerebral blood flow; intracranial pressure. Shock.)

HYPOTENSION is associated with increased mortality in patients who have suffered closed head injury.[1] For those with a Glasgow Coma Score ≤ 8 on admission to the hospital, a systolic blood pressure < 90 mmHg is associated with a risk of poor neurologic outcome 13 times greater than the risk for those in whom systolic arterial pressure exceeds 90 mmHg.[2] Although inadequate cerebral perfusion during shock or subsequent resuscitation might contribute to increased mortality and morbidity, cerebral circulatory changes during acute hemorrhage and resuscitation have not been described in humans. Animal models must provide basic information about changes in intracranial pressure (ICP), cerebral blood flow (CBF), and cerebral metabolism during shock and resuscitation.

Hemorrhagic shock reduces ICP in animals without intracranial pathology[3] and reduces ICP to an even greater extent if an intracranial mass lesion exists.[4,5] Subsequent restoration of blood pressure produces a rapid increase in ICP for which the magnitude of increase depends on the type of resuscitation fluid used.[4,5] Small volumes (4.0–6.0 ml·kg^{-1}) of hypertonic resuscitation solutions produce a minimal increase in ICP in comparison to the large increase associated with larger volumes of conventional crystalloid solutions[3,6] yet produce substantial improvements in blood pressure, cardiac output ($\dot{Q}$), and survival after otherwise lethal hemorrhage.[7–10] Hypertonic solutions are associated with lower ICP than that after administration of isotonic fluids even when used for resuscitation in a volume sufficient to produce hyperdynamic $\dot{Q}$ values.[5,11,12]

Resuscitation with highly hypertonic solutions (7.5% saline) does not improve cortical CBF (measured using ^{133}Xe clearance) in animals with normal ICP[3]; however, the effects on *regional* CBF (rCBF) and ICP have not been reported in animals with hemorrhagic shock and associated intracranial hypertension. The following study compared the effects on ICP and rCBF of resuscitation from hemorrhage with 7.2% hypertonic saline (HS) *versus* 0.8% isotonic saline (SAL) in volumes that provided equal quantities of sodium, in animals with and without intracranial hypertension.

Materials and Methods

Twenty-four mongrel dogs weighing 18–24 kg were cared for according to guidelines established by our institution's Animal Care and Use Committee. Dogs were fasted overnight, anesthetized with intravenous thiopental sodium (8.0 mg·kg^{-1}), and paralyzed with intravenous

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vecuronium (0.2 mg · kg^{-1}). After tracheal intubation, anesthesia was maintained with halothane 0.5% in nitrous oxide and oxygen (60:40). Mechanical ventilation consisted of a tidal volume of 15 ml · kg^{-1} at a rate necessary to maintain normocapnia.

Bilateral brachial artery catheters were inserted, the right for continuous monitoring of systemic arterial blood pressure and the left as a reference organ for CBF determinations using radioactive microspheres. A 7-Fr pigtail catheter was inserted into the left ventricle through the left femoral artery for injection of radioactive microspheres. The right femoral artery was cannulated and used as a second reference organ. A flow-directed, pulmonary artery catheter was placed *via* the right external jugular vein to measure $\dot{Q}$ and pulmonary artery occlusion pressure (PAOP). Hemodynamic pressure monitoring was performed with a Grass 79D polygraph (Grass Instrument Co., Quincy, MA) with Gould-Statham P23 transducers (Gould, Inc., Oxnard, CA). Systemic and pulmonary artery pressures were recorded continuously; PAOP was measured intermittently. Core temperature was monitored continuously by a thermistor on the tip of the pulmonary artery catheter, and normothermia was maintained with the use of a heating pad applied to the trunk and extremities. $\dot{Q}$ was recorded intermittently using an American Edwards 9520A $\dot{Q}$ computer (American Edwards Laboratories, Santa Ana, CA). All transducers were intermittently calibrated at the level of the left atrium.

After splenectomy, animals were turned to the prone "sphinx" position, and the temporalis and occipital musculature were dissected from the skull. After anticoagulation with heparin (500 IU · kg^{-1}), the confluence of the sagittal and lateral sinuses was cannulated using a 3-Fr catheter for intermittent sampling of cerebral venous blood gases and oxygen saturation. An 18-G catheter inserted into the cisterna magna and zeroed at the level of the external auditory meatus (7 cm above left atrial level) provided continuous ICP monitoring. In group 2 animals, the dura was incised through a right temporoparietal burr hole, and the balloon tip of a 7-Fr Foley balloon catheter was inserted subdurally for manipulation of ICP during the shock interval. Preliminary studies had demonstrated that cerebral ventricular, subdural, and cisternal pressures remained comparable if the subdural balloon was slowly inflated to increase ICP to 20 mmHg.

Cerebral Blood Flow Measurement

CBF measurements were obtained using radioactive microspheres (15 μm) labeled with ^{153}Gd, ^{95}Nb, ^{113}Sn, ^{85}Sr, and ^{46}Sc using the organ reference-sample method.[13] Paired reference organ blood samples (ROBS) were withdrawn simultaneously from the right femoral and left brachial arteries using an Edco Model 843 Infusion–Withdrawal Syringe Pump (Edco Scientific, Inc., Chapel Hill, NC).

Prior to injection, microspheres were vortexed for 4 min to insure adequate mixing. The dose of each microsphere type was calculated to yield ≥ 400 microspheres per tissue segment and a minimum of 15,000 counts per ROBS. Injection of each microsphere type was carried out over 15 s. Each ROBS was taken beginning 30 s prior to microsphere injection and was continued for 60 s post-injection, at a withdrawal rate of 2.06 ml · min^{-1}. At the conclusion of the experiment the animals were killed by intravenous injection of saturated potassium chloride, and the brains were removed, dissected, and counted along with the arterial reference samples in a well-type gamma counter (Auto-Gamma 5000, Packard Instruments, Downers Grove, IL). Aliquots of microspheres labeled with each radionuclide were counted along with the blood and tissue samples. Curve stripping, to correct for isotope overlap, was performed using a microcomputer connected to the gamma counter. CBF was derived from the formula:

$$\text{Blood flow} = \frac{C_t \times \text{withdrawal rate} \times 100}{C_r \times Wt} \quad (1)$$

where C_t = counts per minute in the tissue sample, C_r = counts per minute in the reference sample, and Wt = weight of the tissue sample. rCBF was determined for the right cerebral hemisphere, left cerebral hemisphere, and brainstem. In addition, rCBF in the right frontoparietal cortex, immediately adjacent to the subdural balloon (in group 2) and in the analogous region in group 1 was separately analyzed.

Baseline measurements included: CBF, ICP, systolic and diastolic arterial pressures (SAP and DAP), systolic and diastolic pulmonary arterial pressures (PAS and PAD), PAOP, $\dot{Q}$, and serum osmolality (5500 vapor pressure osmometer, Wescor, Inc., Logan, UT). Arterial and cerebral venous *p*H, carbon dioxide tension, and oxygen tension were measured with an IL 1306 blood gas analyzer, and arterial and cerebral oxygen saturation and hemoglobin were analyzed in an IL 282 CO-Oximeter (Instrumentation Laboratory, Lexington, MA). From the collected data, we calculated mean arterial pressure (MAP = DAP + ⅓ [SAP - DAP]), CPP (CPP = MAP − ICP), cerebral arteriovenous oxygen content difference (A − V $\dot{D}_{cere}O_2$), and cerebral oxygen delivery ($\dot{D}_{cere}O_2$) for each hemisphere.

Method of Hemorrhage

Figure 1 summarizes the measurement intervals and interventions. After instrumentation, animals were allowed to stabilize for 30 min, and baseline data were collected. Immediately after baseline data collection and just prior to the initiation of hemorrhagic shock, ICP in ani-

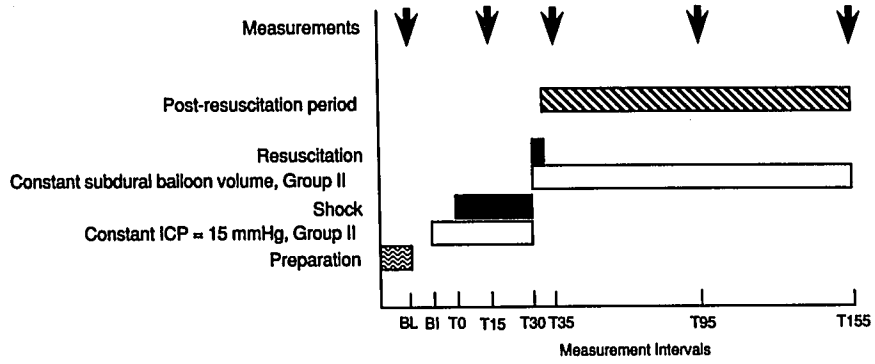

FIG. 1. Summary of experimental sequence. (BL = baseline; BI = balloon inflation.)

mals prepared with subdural balloons (group 2) was gradually increased (~5 min) to 15 mmHg by balloon inflation with saline and maintained at that level with additional inflation volume as necessary throughout the 30-min hemorrhagic shock interval. All animals were then rapidly hemorrhaged *via* the right brachial artery, group 1 to a MAP of 45 mmHg and group 2 to a MAP of 55 mmHg (target CPP = 40 mmHg in both groups), and were maintained by further removal or reinfusion of shed blood. Cerebral and hemodynamic data were obtained halfway through the shock interval, designated as T15 (15 min from the onset of shock). At T30, animals were resuscitated as follows (table 1): group 1 animals (no intracranial mass lesion; n = 12) were randomly assigned to resuscitation with either 7.2% HS (6.0 $ml \cdot kg^{-1}$) or 0.8% SAL (54 $ml \cdot kg^{-1}$). The volumes were chosen to provide equal amounts of sodium. Animals with subdural mass lesions (group 2) also were randomly assigned to the alternative resuscitation fluids as described above. In group 2, just prior to resuscitation, the volume in the subdural balloon was fixed, and ICP was allowed to vary spontaneously during and after resuscitation. Resuscitation fluids were infused intravenously over a 5-min period in both groups. At the conclusion of infusion (T35), a third data set was obtained. Animals were then observed for 2 h with data collection at 60-min intervals, designated as T95 and T155, while lactated Ringer's solution was infused only at a rate sufficient to maintain patency of intravenous catheters.

TABLE 1. Comparison of Body Weight, Shed Blood, and Resuscitation Volume

Group	n	Body Weight (kg)	Blood Loss ($ml \cdot kg^{-1}$)	Volume Infused ($ml \cdot kg^{-1}$)
Group 1				
HS	6	20 ± 1.3	35 ± 2.8	6.0
SAL	6	22 ± 1.1	37 ± 2.4	54.0
Group 2				
HS	6	22 ± 0.8	30 ± 2.5	6.0
SAL	6	22 ± 0.8	33 ± 3.0	54.0

Data are means ± SEM.
HS = 7.2% saline; SAL = 0.8% saline.

STATISTICAL ANALYSIS

The Kruskal-Wallis test was used to assess comparability between groups at baseline and during shock. The primary variables of interest were ICP, CBF, and $D_{cere}O_2$. A multivariate repeated-measures analysis of variance (ANOVA) was performed with the following factors: study (groups 1 and 2), group (HS and SAL), and time.[14] Holm's sequentially rejective multiple test procedure was then used to maintain a significance level of 0.05.[15] To assess study, group, and time differences when an interaction was not present, a multivariate repeated-measures ANOVA and an analysis of covariance were performed on the dependent variables. When a statistically significant effect was evident, Holm's sequentially rejective multiple test procedure was used.

Results

All values in the text, tables, and figures are expressed as means ± standard error of the mean. Mean body weights and volumes of shed blood during hemorrhage for groups 1 (HS and SAL) and 2 (HS and SAL) are listed in table 1. Body weights and shed blood volumes were comparable within group 1 and within group 2. Animals in group 2 required less blood loss because the target MAP exceeded that in group 1.

SYSTEMIC DATA

Both subgroups in each group exhibited comparable MAP at baseline and during shock (table 2). In response to fluid resuscitation (T35), MAP increased similarly with HS and SAL in both groups but was not restored to baseline. SAP was better restored than DAP (table 2).

$\dot{Q}$ (table 2) declined during hemorrhage to approximately 50% of baseline. $\dot{Q}$ increased after resuscitation in all groups; in both groups 1 and 2, $\dot{Q}$ was better restored by SAL ($P < 0.05$). No significant difference between HS and SAL in either group remained at T95 or T155. PAOP was similar among subgroups at all time intervals except T35, at which time PAOP was greater in the

TABLE 2. Major Systemic Variables

	Group	Baseline	T15	T35	T95	T155
MAP (mmHg)	1 HS	113 ± 4	49 ± 4*	82 ± 4	82 ± 10	78 ± 13
	1 SAL	118 ± 9	45 ± 2*	86 ± 5	87 ± 3	81 ± 9
	2 HS	108 ± 6	55 ± 2*	79 ± 8	92 ± 4	73 ± 12
	2 SAL	111 ± 9	54 ± 1*	87 ± 9	95 ± 9	74 ± 14
SAP (mmHg)	1 HS	141 ± 6	77 ± 6	133 ± 10	128 ± 9	114 ± 12
	1 SAL	147 ± 7	67 ± 8	126 ± 4	119 ± 4	115 ± 9
	2 HS	138 ± 8	—	116 ± 7	120 ± 6	103 ± 13
	2 SAL	139 ± 8	—	120 ± 8	123 ± 6	94 ± 12
DAP (mmHg)	1 HS	99 ± 5	34 ± 3	56 ± 4	58 ± 13	50 ± 14
	1 SAL	103 ± 10	30 ± 2	66 ± 6	71 ± 4	65 ± 8
	2 HS	95 ± 6	—	60 ± 8	78 ± 4	58 ± 11
	2 SAL	96 ± 6	—	71 ± 8	80 ± 4	53 ± 10
$\dot{Q}$ ($l \cdot min^{-1}$)	1 HS	3.2 ± 0.4	1.2 ± 0.1	2.9 ± 0.3	1.7 ± 0.1	1.5 ± 0.1
	1 SAL	3.9 ± 0.2	1.4 ± 0.2	4.9 ± 0.5†	2.7 ± 0.3	2.2 ± 0.4
	2 HS	4.1 ± 0.2	1.8 ± 0.1	3.7 ± 0.2	2.2 ± 0.2	2.0 ± 0.3
	2 SAL	3.8 ± 0.3	1.6 ± 0.1	5.3 ± 0.6†	2.5 ± 0.3	1.7 ± 0.3
PAOP (mmHg)	1 HS	4 ± 2	0 ± 1	3 ± 2	3 ± 1	2 ± 1
	1 SAL	5 ± 1	3 ± 1	9 ± 1†	4 ± 1	3 ± 1
	2 HS	5 ± 2	1 ± 1	1 ± 1	1 ± 1	1 ± 2
	2 SAL	5 ± 2	3 ± 1	8 ± 3†	3 ± 1	3 ± 1

Data are means ± SEM.
Note that only MAP was recorded at T15 in group 2.
MAP, SAP, and DAP = mean, systolic, and diastolic arterial pressure, respectively; $\dot{Q}$ = cardiac output; PAOP = pulmonary artery occlusion pressure; HS = 7.2% saline; SAL = 0.8% saline.
* $P < 0.05$ baseline versus T15, group 1 and group 2.
† $P < 0.05$ SAL versus HS, group 1 and group 2.

subgroups that had received SAL ($P < 0.05$). Arterial carbon dioxide tension, *p*H, hemoglobin, and arterial oxygen content were similar among subgroups at all time intervals (table 3). Normothermia was maintained throughout the study. Arterial oxygen tension exceeded 140 mmHg in all animals at all intervals. Serum osmolality (table 4) in the HS subgroup of group 1 increased significantly with fluid resuscitation ($P < 0.05$ HS *vs.* SAL at T95 and T155). Serum osmolality in the HS subgroup in group 2 increased, but not significantly, after resuscitation (table 4).

CEREBRAL HEMODYNAMIC DATA

Intracranial Pressure

ICP (fig. 2) was similar before balloon inflation in all four subgroups and was maintained at 15 mmHg throughout the shock interval in group 2. After resuscitation with SAL, ICP increased markedly at T35 in both groups; in contrast, ICP did not rise after resuscitation in the two HS subgroups (group 1, $P < 0.05$, HS *vs.* SAL; group 2, $P < 0.01$, HS *vs.* SAL). During the 2-h obser-

TABLE 3. Major Systemic Variables

	Group	Baseline	T15	T35	T95	T155
Pa_{CO_2} (mmHg)	1 HS	39.5 ± 0.6	40.2 ± 1.7	40.4 ± 0.9	41.8 ± 2.4	38.9 ± 0.5
	1 SAL	41.2 ± 0.6	41.2 ± 0.4	39.5 ± 0.5	40.8 ± 1.3	41.2 ± 1.4
	2 HS	37.1 ± 0.8	38.4 ± 1.3	36.9 ± 0.8	36.0 ± 0.8	36.7 ± 0.8
	2 SAL	38.4 ± 2.3	38.8 ± 1.0	40.0 ± 0.8	39.3 ± 0.6	39.3 ± 1.6
*p*H	1 HS	7.4 ± 0.0	7.3 ± 0.0	7.2 ± 0.0	7.2 ± 0.0	7.2 ± 0.0
	1 SAL	7.4 ± 0.0	7.3 ± 0.0	7.3 ± 0.0	7.3 ± 0.0	7.2 ± 0.0
	2 HS	7.4 ± 0.0	7.3 ± 0.0	7.3 ± 0.0	7.3 ± 0.0	7.2 ± 0.0
	2 SAL	7.4 ± 0.0	7.3 ± 0.0	7.2 ± 0.0	7.3 ± 0.0	7.2 ± 0.0
Hgb ($g \cdot dl^{-1}$)	1 HS	13.8 ± 1.0	11.3 ± 1.0	8.4 ± 0.7	10.7 ± 0.7	10.2 ± 1.3
	1 SAL	14.1 ± 0.8	11.3 ± 0.7	7.3 ± 0.5	9.7 ± 0.7	10.8 ± 0.9
	2 HS	11.3 ± 0.7	10.1 ± 0.6	7.9 ± 0.4	9.3 ± 0.3	9.6 ± 0.4
	2 SAL	10.7 ± 0.6	9.4 ± 0.6	6.3 ± 0.6	8.3 ± 0.8	8.7 ± 1.1
Ca_{O_2} ($ml \cdot 100\ ml^{-1}$)	1 HS	18.8 ± 1.2	15.6 ± 1.2	11.8 ± 0.9	14.9 ± 0.9	14.3 ± 1.7
	1 SAL	19.5 ± 1.1	15.7 ± 0.9	10.3 ± 0.6	13.5 ± 0.9	14.9 ± 1.2
	2 HS	14.7 ± 0.7	13.3 ± 0.6	10.8 ± 0.7	12.5 ± 0.3	12.5 ± 0.4
	2 SAL	14.7 ± 1.1	12.9 ± 0.9	9.0 ± 0.9	11.6 ± 1.2	12.0 ± 1.6

Data are means ± SEM.
Hgb = hemoglobin; Ca_{O_2} = arterial oxygen content; HS = 7.2% saline; SAL = 0.8% saline.

TABLE 4. Serum Osmolality (mOsm · kg^{-1})

		Baseline	T95	T155
Group 1	7.2% HS	292 ± 12	318 ± 6*†	324 ± 4*†
Without mass	0.8% SAL	292 ± 7	281 ± 14	299 ± 0
Group 2	7.2% HS	292 ± 13	303 ± 4	309 ± 2
With mass	0.8% SAL	289 ± 9	290 ± 5	292 ± 7

* $P < 0.05$ HS *versus* SAL, group 1.
† $P < 0.05$ baseline *versus* T95, baseline *versus* T155, group 1.

vation period, ICP in group 1-SAL decreased over time to nearly that in group 1-HS, which remained less than baseline preshock values. By T95, ICP had increased slightly in group 2-HS but still averaged < 20 mmHg, whereas ICP in group 2-SAL decreased only slightly, from a maximal pressure of 34 ± 3 mmHg at T35 to 28 ± 3 mmHg. There were no significant differences between HS and SAL in group 2 at T95 or T155.

Cerebral Perfusion Pressure

CPP (fig. 3) followed the same general pattern as MAP. CPP was not restored to baseline in either group by HS or SAL after resuscitation. No statistical differences in CPP were detected between HS and SAL in group 1 or 2 at any time period.

Regional CBF and Oxygen Transport

rCBF in the right frontoparietal cortex (adjacent to the subdural balloon in group 2 and in the analogous region in group 1) was not significantly different between group 1-HS and group 1-SAL or between group 2-HS or group 2-SAL at baseline or during shock (table 5). At T35, rCBF was lower in the SAL subgroups than in the HS subgroups ($P < 0.05$). rCBF declined significantly after resuscitation in group 2-SAL ($P < 0.001$, T155 *vs.* T35) but not in group 2-HS.

There were no differences in right or left hemispheric rCBF between HS or SAL in either group 1 or 2 at baseline or during shock (table 5). In group 1 (no mass lesion), fluid resuscitation increased rCBF in the right cerebral hemisphere at T35 above baseline with HS and to baseline with SAL (P = not significant, HS *vs.* SAL). In group 2, rCBF in the right cerebral hemisphere remained lower than baseline after administration of either fluid. HS did increase rCBF in the right cerebral hemisphere somewhat, in contrast to SAL, which did not improve blood flow to the right hemisphere ($P < 0.05$, HS *vs.* SAL at T35 and T95). Right cerebral hemispheric blood flow in group 2-SAL continued to decline during the observation period to 8 ± 5 ml · 100 g^{-1} · min^{-1} ($P < 0.001$, T155 *vs.* baseline). In group 2, left cerebral hemispheric blood flow was restored to baseline by HS; SAL produced minimal improvement. The difference in group 2 left cerebral hemispheric blood flow between HS and SAL at T95 approached significance ($P = 0.06$).

Brainstem blood flow (table 5) was similar between HS and SAL in groups 1 and 2 at baseline and during shock; changes during hemorrhage in either group were insignificant. Resuscitation increased brainstem blood flow immediately after infusion of HS and SAL in both groups, to baseline or greater. Brainstem blood flow did not significantly decrease in any subgroup throughout the experimental period.

$A - V\dot{D}_{cere}O_2$ in both groups 1 and 2 increased during hemorrhage, decreased at T35, and then remained

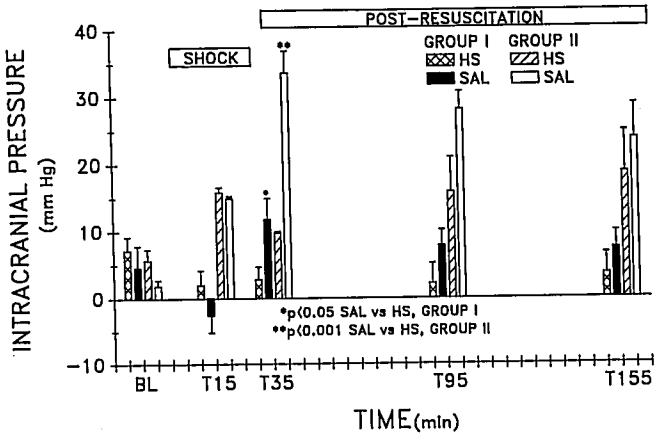

FIG. 2. Response of intracranial pressure after resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS) or 0.8% saline (SAL) in animals without (group 1) and with (group 2) a right hemispheric intracranial mass. Intracranial hypertension induced by inflation of the right hemispheric subdural balloon accompanied hemorrhage in group 2. BL = baseline.

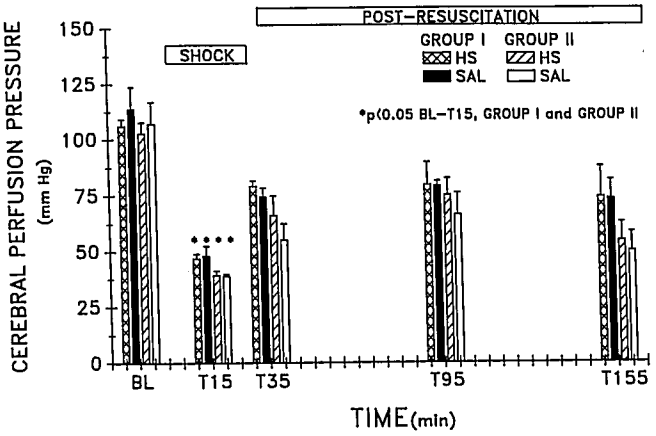

FIG. 3. Changes in cerebral perfusion pressure after resuscitation from hemorrhagic shock with hypertonic 7.2% saline (HS) or 0.8% saline (SAL) in animals without (group 1) and with (group 2) a right hemispheric intracranial mass. BL = baseline.

TABLE 5. Regional Cerebral Blood Flow

	Group	Baseline	T15	T35	T95	T155
Right frontoparietal cortex ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)**	1 HS	50 ± 6	44 ± 9	80 ± 18	44 ± 6	37 ± 5
	1 SAL	40 ± 2	34 ± 3	50 ± 6	40 ± 4	39 ± 4
	2 HS	68 ± 15	30 ± 13	44 ± 10	48 ± 16	29 ± 10
	2 SAL*	66 ± 10	14 ± 3	16 ± 7	10 ± 5	7 ± 4
Right cerebral hemisphere ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)	1 HS	52 ± 6	46 ± 9	81 ± 17	50 ± 8	41 ± 6
	1 SAL	42 ± 3	36 ± 3	53 ± 7	44 ± 5	42 ± 5
	2 HS	66 ± 14	34 ± 13	50 ± 10	45 ± 13	30 ± 9
	2 SAL*	59 ± 7	18 ± 3†	21 ± 7†	11 ± 5†	8 ± 5†‡
Left cerebral hemisphere ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)	1 HS	51 ± 6	45 ± 10	77 ± 16	46 ± 9	41 ± 6
	1 SAL	45 ± 3	37 ± 3	53 ± 7	44 ± 6	42 ± 5
	2 HS	67 ± 15	49 ± 13	66 ± 15	44 ± 10	33 ± 10
	2 SAL§	64 ± 10	37 ± 6	41 ± 9	18 ± 6†	12 ± 7†‡
Brainstem ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)	1 HS	45 ± 5	41 ± 9	77 ± 17	53 ± 11	48 ± 6
	1 SAL	44 ± 5	34 ± 3	49 ± 8	42 ± 7	39 ± 5
	2 HS	54 ± 11	42 ± 8	66 ± 11	43 ± 9	38 ± 9
	2 SAL*	54 ± 4	41 ± 6	63 ± 9	37 ± 11	23 ± 3¶

Data are means ± SEM. HS = 7.2% saline; SAL = 0.8% saline.
* $P < 0.05$ by ANOVA, group 2-SAL *versus* group 2-HS.
† $P < 0.01$ between group 1-SAL and group 2-SAL at specific intervals.
‡ $P < 0.001$ T155 *versus* baseline.
§ $P = 0.06$ by ANOVA, group 2-SAL *versus* group 2-HS.
¶ $P < 0.02$ T155 *versus* baseline.
** In group 2, the subdural balloon was applied over the right frontoparietal cortex.

greater for the remainder of the experiment with no significant intragroup difference (table 6).

Kruskal-Wallis testing excluded significant differences in regional cerebral oxygen transport ($\dot{D}_{cere}O_2$) in the right frontoparietal cortex, right hemispheric cortex, and left hemispheric cortex at baseline and during shock (table 6). Induction of hemorrhage decreased $\dot{D}_{cere}O_2$ in all subgroups. In the right frontoparietal cortex, $\dot{D}_{cere}O_2$ was greater in group 2-HS than in group 2-SAL at T35 and T95 ($P < 0.05$). In both groups 1-SAL and 2-SAL, right frontoparietal $\dot{D}_{cere}O_2$ decreased significantly from baseline to T155 ($P < 0.001$); the decreases in groups 1-HS and 2-HS were not significant. Right and left hemispheric $\dot{D}_{cere}O_2$ in group 1-HS increased to baseline with resuscitation and then gradually decreased. The increase of CBF at T35 was sufficient to offset the acute decline in arterial oxygen content produced by hemodilution. In group 2, right and left hemispheric $\dot{D}_{cere}O_2$ increased slightly at T35 in group 2-HS and then decreased. Right hemispheric $\dot{D}_{cere}O_2$ was significantly greater in group 2-

TABLE 6. Cerebral Oxygen Delivery

	Group	Baseline	T15	T35	T95	T155
Right frontoparietal cortex ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)††	1 HS	9.4 ± 1.3	6.5 ± 0.9	9.1 ± 1.9	6.5 ± 0.7	5.1 ± 0.5
	1 SAL	7.7 ± 0.5	5.2 ± 0.3	5.0 ± 0.4	5.0 ± 0.2	5.6 ± 0.5*
	2 HS	9.9 ± 1.7	4.1 ± 1.6	4.8 ± 1.1	6.2 ± 2.0	3.9 ± 1.3
	2 SAL†	9.8 ± 1.7	2.0 ± 0.4	1.6 ± 0.8‡	1.2 ± 0.6‡	1.0 ± 0.6§
Right cerebral hemisphere ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)	1 HS	9.8 ± 1.1	6.7 ± 0.9	9.2 ± 1.8	7.2 ± 1.0	5.7 ± 0.7
	1 SAL	8.2 ± 0.6	5.6 ± 0.3	5.3 ± 0.4	5.5 ± 0.3	6.1 ± 0.5*
	2 HS	9.6 ± 1.6	4.5 ± 1.5	5.4 ± 1.1	5.8 ± 1.6	3.9 ± 1.2
	2 SAL¶	8.8 ± 1.3	2.5 ± 0.5	2.1 ± 0.8‡**	1.5 ± 0.7‡**	1.2 ± 0.7§**
Left cerebral hemisphere ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)	1 HS	9.5 ± 1.1	6.6 ± 1.1	8.7 ± 1.6	6.6 ± 1.1	5.5 ± 0.5
	1 SAL	8.6 ± 0.6	5.8 ± 0.3	5.4 ± 0.4	5.6 ± 0.3	6.1 ± 0.5*
	2 HS	9.8 ± 1.7	6.7 ± 1.6	6.9 ± 1.5	5.6 ± 1.4	4.4 ± 1.4
	2 SAL††	9.5 ± 1.7	5.0 ± 1.0	3.7 ± 0.9	2.3 ± 0.7**	1.7 ± 1.0*,**
Cerebral A–V$\dot{D}_{O_2}$ ($ml \cdot 100\ ml^{-1}$)	1 HS	5.3 ± 0.9	7.6 ± 1.2	4.2 ± 0.4	6.7 ± 0.9	7.4 ± 0.9
	1 SAL	5.6 ± 0.5	8.1 ± 0.4	5.0 ± 0.6	6.7 ± 0.6	7.8 ± 1.1
	2 HS	4.9 ± 0.7	7.0 ± 0.6	4.9 ± 0.4	6.3 ± 0.6	7.0 ± 0.9
	2 SAL	4.9 ± 0.6	7.0 ± 0.5	4.4 ± 0.4	5.7 ± 0.5	7.1 ± 1.2

Data are means ± SEM. HS = 7.2% saline; SAL = 0.8% saline.
* $P < 0.001$ T155 *versus* baseline.
† $P < 0.06$ by ANOVA, group 2-SAL *versus* group 2-HS.
‡ $P < 0.05$ group 2-SAL *versus* group 2-HS at specific interval.
§ $P = 0.0001$ T155 *versus* baseline.
¶ $P < 0.01$ by ANOVA, group 2-SAL *versus* group 2-HS.
** $P < 0.01$ group 1-SAL *versus* group 2-SAL.
†† $P = 0.05$ by ANOVA, group 2-SAL *versus* group 2-HS.
‡‡ In group 2, the subdural balloon was applied over the right frontoparietal cortex.

HS than in group 2-SAL at T35 and T95 ($P < 0.05$). Group 2-SAL showed progressive deterioration in right and left hemispheric $\dot{D}_{cere}O_2$ after resuscitation ($P < 0.01$ T155 *vs.* baseline in both groups).

Discussion

There is a growing interest in the use of hypernatremic crystalloid solutions for intravascular volume replacement after hemorrhage. Such solutions can 1) effectively restore $\dot{Q}$ and organ blood flow in total fluid volumes less than those of isotonic crystalloid solutions[3,7,8,11,16,17]; 2) improve myocardial contractility[18]; and 3) lower pulmonary artery pressures and systemic resistance.[19–21] Low cost and long shelf life make hypertonic solutions attractive for acute resuscitation after major trauma either in the hospital or at the scene of the injury.

The major potential physiologic advantage of hypertonic resuscitation solutions is that ICP is not increased as it is by conventional resuscitation solutions such as lactated Ringer's solution, a slightly hypotonic fluid. However, lower ICP alone is not a sufficient justification for hypertonic resuscitation. CBF depends on CPP which in turn is more powerfully influenced by MAP than by ICP because of the greater magnitude of MAP.[3] Therefore, before hypertonic solutions are used for resuscitation, it is essential to determine if CBF is improved, particularly under circumstances in which reduced intracranial compliance amplifies the cerebral physiologic difference between hypertonic and slightly hypotonic fluids.

These data further clarify the cerebral physiologic effects of hypertonic resuscitation solutions when compared to comparable quantities of sodium administered as slightly hypotonic solutions. At comparable levels of CPP in both groups immediately after resuscitation, the hypertonic solution was associated with higher CBF than was the slightly hypotonic crystalloid solution, although that tendency rapidly disappeared in animals without intracranial hypertension. However, in animals with intracranial mass lesions, the difference in rCBF persisted throughout the 120-min postresuscitation interval, despite comparable increases in CPP. In fact, in both subgroups of group 2, CPP was restored to a level associated with preserved autoregulation in animals without intracranial pathology.[22]

These data also expand existing information regarding the effects of hypertonic resuscitation solutions on ICP. The effects of fluid resuscitation on ICP require consideration of several factors, including cerebral arterial and venous blood volume, brain tissue volume (*i.e.*, water content), and cerebrospinal fluid volume. The current data do not address differential effects of slightly hypotonic and hypertonic fluids on each component of intracranial volume. Hypertonic salt solutions reduce brain water and therefore tend to reduce ICP, regardless of whether antecedent shock is present.[3,5,11,12,23] The permeability of intact blood–brain barrier to sodium is very low. Therefore, changes in serum sodium and associated changes in osmolality cause rapid changes in ICP and in brain water. Isovolemic hemodilution with hypertonic lactated saline (252 $mEq \cdot l^{-1}$ Na^+), in comparison to 0.9% saline, decreases ICP and brain water.[23] Zornow and colleagues used plasmapheresis to acutely reduce serum osmolality or oncotic pressure in rabbits and demonstrated that small decreases in serum osmolality increased both ICP and brain water.[24]

The major objective of the current study was to characterize further the cerebral hemodynamic changes that occur after resuscitation with HS after severe hemorrhage associated with reduced intracranial compliance. In this model, 6 $ml \cdot kg^{-1}$ of 7.2% saline replaced only 15–20% of the shed blood volume, in marked contrast to conventional crystalloid replacement therapy, which requires replacement of two to three times the blood loss. We speculate that these volumes produced less change in osmolality in the HS animals in group 2 than in those in group 1 for two reasons. First, less blood was removed from group 2 animals to reduce MAP because the target level of MAP was greater. Therefore, the greater remaining blood volume may have exerted a greater diluting effect. Second, because both $\dot{Q}$ and MAP were lower in group 1 animals, the systemic effects of more profound shock may have altered the distribution of sodium both during shock and after fluid administration.

The potential value of hypertonic saline as a resuscitation fluid after hemorrhagic shock with severe central nervous system injury is evident from the reduction in ICP seen immediately after resuscitation, since it is well established (and confirmed in the current experiments) that increases in ICP commonly occur after conventional crystalloid resuscitation. The effect of HS on ICP was apparent throughout the postresuscitation period in group 2-HS; at no time did ICP exceed 20 mmHg, as it did consistently in group 2-SAL. Because inflation of a subdural balloon, unlike clinical or experimental head injury, is not associated with acceleration–deceleration trauma, it is possible that the ability of the intracranial contents to compensate for an increase in intracranial volume was greater in these animals than could be expected after a concussion. Nonetheless, it is readily apparent that HS is superior to isotonic crystalloid solutions in minimizing ICP increases due to rapid fluid infusion after hemorrhage.

HS has been associated with a lower ICP than have isotonic salt solutions when used for resuscitation from hemorrhagic shock.[3,5,11,12] Prough and colleagues compared a single bolus of 7.5% HS (6.0 $ml \cdot kg^{-1}$) to lactated

Ringer's solution (60 ml · kg^{-1}) after a 30-min shock interval produced by blood loss of approximately 40 ml · kg^{-1} in mongrel dogs.[3] HS was associated with a significantly lower postresuscitation ICP than was lactated Ringer's solution, but with a similar, reduced level of CBF and cerebral oxygen transport. The superior rCBF achieved with HS in the current study may reflect the greater precision of measurements of CBF using radiolabeled microspheres in comparison to the ^{133}Xe clearance technique used in our earlier study.[3] In addition, microsphere measurements require less time to perform and therefore may have more accurately identified an early transient peak in CBF.

Gunnar and colleagues compared resuscitation from hemorrhagic shock using 3.0% saline, 0.9% saline, or a 10% solution of dextran 40.[11] ICP in the group that had received 0.9% saline consistently exceeded ICP in the group that had received 3.0% saline.[11] In a subsequent study, in animals subjected to hemorrhagic shock combined with epidural balloon inflation, ICP increased dramatically in a group that had received 0.9% saline and increased little in a group that had received 3.0% saline.[5] However, in contrast to the current study, Gunnar and colleagues inflated the balloon prior to shock and then during shock permitted ICP to decline.[5] Because ICP decreased during the shock interval, the magnitude of associated cerebral ischemia may well have been less. CPP had increased to approximately 65 mmHg by the end of the shock interval. In a subsequent publication, a resuscitation regimen equivalent to the previous one produced no differences in CBF.[12] However, as before, ICP was permitted to decline during hemorrhage, resulting in a higher CPP during the shock interval.

With regard to the current study, perhaps the most important observation of Gunnar and colleagues is that shock combined with inflation of an epidural balloon produces increased permeability of the blood–brain barrier to Evans blue dye, an albumin-bound tracer.[5] As noted above, CPP during shock in that study was substantially greater, increasing from a low of approximately 40 mmHg at the beginning of shock to approximately 65 mmHg by the end of the shock interval. Consequently, we speculate that in the current study blood–brain barrier function also may have been severely disturbed by cerebral hypoperfusion. That speculation requires further investigation.

In the current study, right hemispheric CBF was better restored in group 2-HS, but this effect did not appear to be due to improved CPP alone, since CPP was similar in both subgroups at all time periods. In these experiments, the inability of an adequate CPP to maintain CBF suggests a reduced ability of the brain vessels to compensate (*i.e.*, to autoregulate). Several explanations may account for improved right hemispheric CBF after hypertonic solutions. First, HS, by decreasing brain water, may limit local brain tissue pressure increases in a manner analogous to mannitol.[25,26] A second possible mechanism is direct cerebral vasodilatation by HS,[27,28] which directly dilates pial vessels when topically applied.[28]

As noted by Todd *et al.*,[23] many trauma patients suffer major neurologic injuries in addition to severe systemic injury and hemorrhage. Intracranial injury complicates fluid resuscitation because of the potential for adverse cerebral hemodynamic effects. Although hypertonic solutions appear to reduce ICP and improve CBF, severe hypernatremia may be associated with confusion, coma,[29] blood–brain barrier disruption,[30] and cerebral dehydration leading to possible intracranial hemorrhage. These effects appear to represent a negligible risk if hypertonicity develops in association with hypertonic resuscitation, in contrast to hypertonicity that develops as a consequence of pathologic loss of free water.

We conclude that HS solutions offer advantages over conventional slightly hypotonic and isotonic solutions in resuscitation after hemorrhage combined with a subdural mass lesion. We have shown improvement in global and regional CBF and also demonstrated that systemic hemodynamics are sufficiently improved to maintain adequate tissue perfusion until more definitive therapy of shock can be instituted. Further studies are necessary to determine if acute resuscitation with HS limits neurologic impairment in severely traumatized patients with central nervous system injury.

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