Opposed effects of hypertonic saline on contusions and noncontused brain tissue in patients with severe traumatic brain injury*

Thomas Lescot, MD; Vincent Degos, MD; Abderrezak Zouaoui, MD, PhD; Françoise Préteux, PhD; Pierre Coriat, MD; Louis Puybasset, MD, PhD

Objective: **The aim of this study was to quantify the effect of hypertonic saline solution on contused and noncontused brain tissue in patients with traumatic brain injury. We hypothesize that hypertonic saline would increase the volume of brain contusion while decreasing the volume of noncontused hemispheric areas.**

Design: **Prospective observational study.**

Setting: **Neurosciences critical care unit of a university hospital.**

Patients: **Fourteen traumatic brain injury patients with increased intracranial pressure.**

Interventions: **A computed tomography scan was performed before and after a 20-min infusion of 40 mL of 20% saline.**

Measurements and Main Results: **The volume, weight, and specific gravity of contused and noncontused hemispheric areas were assessed from computed tomography DICOM images by using a custom-designed software (BrainView). Physiologic variables and natremia were measured before and after infusion. Hypertonic saline significantly increased natremia from 143 ± 5 to 146 ± 5 mmol/L and decreased intracranial pressure from 23 ± 3 to 17 ± 5 mm Hg. The volume of the noncontused hemispheric areas decreased by 13 ± 8 mL whereas the specific gravity increased by 0.029 ± 0.027%. The volume of contused hemispheric tissue increased by 5 ± 5 mL without any concomitant change in density. There was a wide interindividual variability in the response of the noncontused hemispheric tissue with changes in specific gravity varying between −0.0124% and 0.0998%.**

Conclusions: **Three days after traumatic brain injury, the blood-brain barrier remains semipermeable in noncontused areas but not in contusions. Further studies are needed to tailor the use of hypertonic saline in patients with traumatic brain injury according to the volume of contusions assessed on computed tomography. (Crit Care Med 2006; 34:3029–3033)**

KEY WORDS: head trauma; specific gravity; computed tomography; contusion; blood-brain barrier

Hypertonic saline (HS) used at various concentration (3–23.4%) has been consistently shown to decrease intracranial pressure (ICP) and cerebral water content in human traumatic brain injury (TBI) (1, 2). The mean pressure drop is usually 40% (3). HS is still used as a second-line therapy in adults (4) and children (5) with exhausted response to mannitol and barbiturates. Experimentally, HS is more efficient in reducing ICP than equiosmolar doses of mannitol (6). In addition, HS might also be beneficial to the immune system by modulating cellular immune function after trauma and restoring the immune function of healthy T cells (7–9).

However, the patient population that is most likely to respond to HS needs to be further defined. From a theoretical point of view, it can be expected that HS is effective only in the areas of the brain where the blood-brain barrier (BBB) is still functional after trauma. There are numerous arguments in favor of a profound alteration of the BBB in contusion appearing areas on CT (10–12) in part secondary to regional ischemia (11, 13–15). This study was thus designed to evaluate the regional effects of hypertonic saline on contused and noncontused brain tissue after TBI. Our hypothesis was that HS would increase the volume of brain contusion while decreasing the volume of the noncontused areas. This was done by comparing global and regional brain volume, weight, and specific gravity, as assessed by a recently described software (16) computing these variables out of computed tomography (CT) images, before and after HS bolus administration in a series of 14 patients with severe head trauma.

METHODS

Patients. We prospectively included 14 patients who were admitted to our neurosurgical intensive care unit with severe traumatic brain injury or nonsevere traumatic brain injury with secondary neurologic deterioration requiring intubation, mechanical ventilation, and ICP monitoring as part as their management. Inclusion criteria were the combination of an ICP >20 mm Hg for >15 mins, a natremia <155 mmol·L^{-1}, and a delay since the onset of head trauma of 1–5 days. Patients were not included if transportation to the CT suite was considered too dangerous by the clinician in charge of the patient because of a permanently increased ICP or because of hemodynamic instability. This study received ethical approval by our local institutional review board (CCPPRB Pitié-Salpêtrière's Hospital), and written informed consent was obtained from the patient's next of kin.

*See also p. 3057.

From the Department of Anesthesiology and Critical Care (TL, VD, PC, LP) and Department of Neuroradiology (AZ), Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris; Université Pierre et Marie Curie-Paris 6, France; and the Artemis Project Unit, Institut National des Télécommunications, Evry, France (FP).

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All patients were orotracheally intubated and mechanically ventilated and had an internal ventricular drain inserted after they met international criteria for ICP monitoring. ICP was monitored through the external ventricular derivation catheter (Sophysa, Orsay, France), connected to a calibrated pressure transducer (Transpac, Abbott, Sligo, Republic of Ireland), zeroed at the external eye angle, and inserted during the first 24 hrs after trauma. Doppler of the mean cerebral arteries were performed at least once a day. Patients were treated according to our intensive care guidelines including 30° head up positioning, cerebrospinal fluid drainage if ICP increased above 20 mm Hg, cerebral perfusion pressure maintained between 70 and 80 mm Hg, pulsatility index maintained <1.2 through the use of fluid loading and continuous infusion of norepinephrine, sedation with a continuous intravenous infusion of sufentanil and midazolam and propofol as required for ICP control, and maintenance of normocapnia, normoxia, and normoglycemia.

Study Design. After a period of stabilization in the CT suite, a first cerebral CT scan (CT 1) was performed on a high-speed advantage CT scan (GE Medical Systems). On completion of imaging, an intravenous infusion of 40 mL of 20% HS was injected over 20 mins through a central venous catheter while the patient was maintained sedated and ventilated on the CT stretcher. Great care was taken to maintain the patient perfectly still during the infusion period. A second CT (CT 2) was performed 2 mins after HS infusion ended. The intraventricular drainage was clamped and the infusion rates of norepinephrine and sedation were maintained unchanged during the study period. Heart rate, mean arterial blood pressure, intracranial pressure ICP, and end-tidal CO_2 were measured before each CT and just before and right after HS infusion. Natremia was measured in the intensive care unit before and after transportation to the CT.

Images Analysis. CT images were acquired as 5-mm-thick contiguous slices and analyzed using a custom-designed software package (BrainView 1.8) recently described by our group (16). BrainView provides semiautomatic tools for brain analysis and quantification from images obtained from cerebral CT scan. For each CT image, BrainView input a series of continuous axial scans of the brain. It then automatically excluded extracranial compartments on each CT section by means of a mathematical morphology-based algorithm. Interactive slice-by-slice segmentation allowed selection of different anatomical territories indexed throughout the whole sequence.

As a first step, the overall intracranial content was delineated. Two subsets of analysis were then performed: The first one was on different anatomical segments: left and right hemispheres together called "hemispheres," brainstem, cerebellum, and intraventricular and cisternal cerebrospinal fluid. The second analysis focused on contused and noncontused hemispheric tissue. The hemispheric contused tissue was identified and delineated on each slice using the thresholding function of the image analysis software. The contusion was definite as abnormal hemispheric tissue including the hyperdense core (radiologic attenuation >40 HU) and the hypodense pericontusional tissue (radiologic attenuation <20 HU) together (Fig. 1). In case of plurifocal contusions, all of them were delineated on each slice. Noncontused hemispheric tissue was identified as normal appearing tissue on each slice.

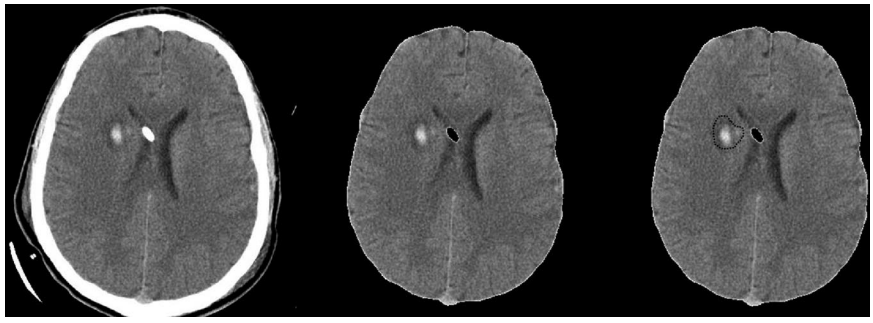

Figure 1. Original computed tomography scan image (*left panel*). Automatic isolation of the intracranial compartment by the software (*middle panel*). Isolation of the contused and noncontused tissue (*right panel*). Note that the intraventricular derivation catheter is excluded from intracranial compartment.

For each compartment of a known number of voxels, the volume, weight, and specific gravity were computed using the following equations:

1. Volume of the voxel = (size of the pixel)^2 × section thickness.
2. Weight of the voxel = (1 + CT/1000) × volume of the voxel, where CT is the CT number of the voxel.
3. Volume of the compartment = number of voxels × volume of the voxel.
4. Weight of the compartment = summation of the weight of each individual voxel included in the compartment.
5. Specific gravity of the compartment = weight of the compartment/volume of the compartment. The specific gravity is expressed as a physical density in g/mL.

Patients were classified according to the response of their noncontused areas to HS. Responders were defined *a priori* as patients having a change of the specific gravity (SG) >0.03%. This threshold was chosen as the one that discriminates half of the patients included.

Statistical Analysis. The data are expressed as mean ± SD for Gaussian and non-Gaussian variables. The effects of HS on the physiologic variables measured and on the different anatomical compartments (hemispheres, brainstem, cerebellum, cerebrospinal fluid) were analyzed by paired Student's *t*-test. The effects of HS on contused and noncontused areas were compared by a two-way analysis of variance for two within factors: factor "HS" (before, after) and factor "Contusion" (contused areas vs. noncontused areas). A significant interaction between these two factors indicates that HS has a different effect in contused areas and noncontused areas. The change in the weight of contusion according to its initial volume assessed in percentage of the hemispheres was analyzed by linear regression analysis. Statistical analyses were performed using JMP IN 5.1 statistical software (SAS Institute, Cary, NC). Considering the fact that weight was derived from the computation of volume and SG, the significance level was fixed at 2.5% to accommodate two independent tests.

RESULTS

Physiologic Variables. Fourteen patients (12 male, two female) were prospectively studied 3 ± 2 days after injury (1–5 days). Ages ranged from 18 to 69 (36 ± 15) years. The Glasgow Coma Scale score at the scene of accident ranged from 4 to 14 with a median score of 7 (Table 1).

At baseline, heart rate was 68 ± 12 per min, mean arterial blood pressure was 103 ± 9 mm Hg, and ICP was 23 ± 3 mm Hg. HS significantly decreased ICP by 6 ± 3 mm Hg ($p < 001$) with no concomitant effect on heart rate, mean arterial blood pressure, cerebral perfusion pressure, or end-tidal CO_2 (data not shown). HS significantly increased natremia by 3 ± 1 from 143 ± 5 mmol/L ($p < .01$).

Effects of HS on Anatomical Structures. The effects of HS differed between the various anatomical regions of the brain. HS decreased the volume of the hemispheres while increasing their specific gravity (Table 2). No significant changes in the weight, volume, and SG of the cerebellum, brainstem, and cerebrospinal fluid were noted.

Effects of HS on Contused and Noncontused Tissue. HS had opposite effects on noncontused and contused hemispheric areas (Table 3, Fig. 2, significant interaction, $p < .0001$). HS decreased the

Table 1. Patient details

Age, Yrs	Gender	Injury Mechanism	GCS	Marshall	Surgery	SAPS II	LOS	GOS
69	M	Traffic injury	7	NEML		69	44	2
36	M	Traffic injury	7	EML	LSDH	38	9	1
37	M	Assault	7	3		41	28	5
18	M	Traffic injury	7	EML	RSDH, LEDH	39	28	3
40	M	Fall	6	NEML		41	20	5
20	F	Traffic injury	11	2		40	9	4
21	M	Traffic injury	8	3		47	28	3
22	F	Traffic injury	8	2		42	39	4
45	M	Fall	7	EML	REDH	48	27	3
57	M	Traffic injury	7	2		48	75	1
31	M	Assault	7	2		41	7	1
33	M	Fall	10	EML	LSDH	43	27	3
26	M	Traffic injury	14	NEML		28	11	1
44	M	Fall	4	EML	LSDH	67	10	1

GCS, Glasgow Coma Scale score; SAP, Simplified Acute Physiology Score; LOS, length of stay in the intensive care unit; GOS, Glasgow Outcome Score at ICU discharge (5 = good recovery; 1 = death), NEML, nonevacuated mass lesion; EML, evacuated mass lesion; LSDH, left subdural hematoma; RSDH, right subdural hematoma; LEDH, left extradural hematoma; REDH, right extradural hematoma.

Table 2. Effects of hypertonic saline on weight, volume, and specific gravity (SG) of the different anatomical structures

	Before HS Infusion	After HS Infusion	*p*
Hemispheres			
Weight, g	1161 ± 76	1153 ± 75	<.01
Volume, mL	1123 ± 76	1115 ± 75	<.01
SG, g/mL	1.0338 ± 0.0032	1.0341 ± 0.0031	<.01
Brainstem			
Weight, g	27 ± 6	26 ± 6	NS
Volume, mL	26 ± 6	25 ± 6	NS
SG, g/mL	1.0289 ± 0.0019	1.0294 ± 0.0021	NS
Cerebellum			
Weight, g	131 ± 14	133 ± 14	NS
Volume, mL	126 ± 14	128 ± 13	NS
SG, g/mL	1.0359 ± 0.0037	1.0363 ± 0.0035	NS
Cerebrospinal fluid			
Weight, g	43 ± 31	43 ± 31	NS
Volume, mL	44 ± 32	43 ± 31	NS
SG, g/mL	1.0164 ± 0.0057	1.0168 ± 0.0051	NS

HS, hypertonic saline; NS, not significant.

Table 3. Effects of hypertonic saline on weight, volume, and specific gravity (SG) of the contused and noncontused hemispheric areas

	Before HS Infusion	After HS Infusion	*p*
Normal appearing hemispheres			
Weight, g	1096 ± 91	1082 ± 93	<.0001
Volume, mL	1060 ± 90	1047 ± 92	<.0001
SG, g/mL	1.0336 ± 0.0029	1.0339 ± 0.0029	<.005
Contusion appearing hemispheres			
Weight, g	65 ± 58	70 ± 61	<.001
Volume, mL	62 ± 55	68 ± 59	<.001
SG, g/mL	1.0364 ± 0.0069	1.0365 ± 0.0070	NS

HS, hypertonic saline; NS, not significant.

volume of the noncontused hemispheric tissue by 13 ± 8 mL while increasing the SG by 0.029 ± 0.027%. There was a wide variability in the response of noncontused hemispheric tissue to HS, with changes in SG varying between −0.0124% and 0.0998% (Fig. 3). Age, initial Glasgow Coma Scale Score, initial Simplified Acute Physiology Score II, mechanism of accident, delay between trauma and CT, initial SG, and ICP decrease were similar between responders and nonresponders to HS.

The volume of the contused tissue ranged from 3 to 157 mL (62 ± 55 mL). HS increased the volume of contused hemispheric tissue by 5 ± 5 mL without any concomitant change in density. The increase of the contusion's weight with HS injection was significantly related to baseline contusion volume expressed as a percentage ($r^2 = .62$, $p = .01$) (Fig. 4).

DISCUSSION

The main result of the study is the observation of a differential effect of HS on noncontused and contused hemispheric areas. HS consistently decreased the weight of the noncontused areas while increasing the SG, indicating a net decrease in water content and consequently a functional BBB. At the opposite, HS always increased the weight of contusion. Interestingly, the response to HS, quantified as the change in SG in normally appearing areas on CT, varied to a great extent among TBI patients.

Different types of edema coexist in TBI patients: vasogenic edema due to BBB breakdown, cytotoxic edema secondary to ischemic insult, or cellular edema resulting from neurotoxic insult. Clearly, there is a time and regional dependency in the occurrence of these different edema subtypes. There are many experimental arguments showing that the BBB is temporarily damaged by trauma. Time window studies indicate that the barrier seals within a few hours following severe head injury (17). In the experimental model of Barzo et al. (18), permeability of the BBB returned to control values as soon as 30 mins after the head trauma. Tanno et al. (19) also observed a pronounced abnormal permeability to immunoglobulin G and horseradish peroxidase occurring within the first hour after injury that was widespread throughout both hemispheres after a lateral, fluid percussive brain injury in the rat. Maximal permeability occurred at 1 hr after injury. This was confirmed by Baldwin et al. (10). In humans, this early, transient, and diffuse opening of the BBB might increase the brain SG since the edematous fluid could have a specific gravity higher than the brain parenchyma. This might account for the increased SG observed in human TBI (16). The state of the BBB after this

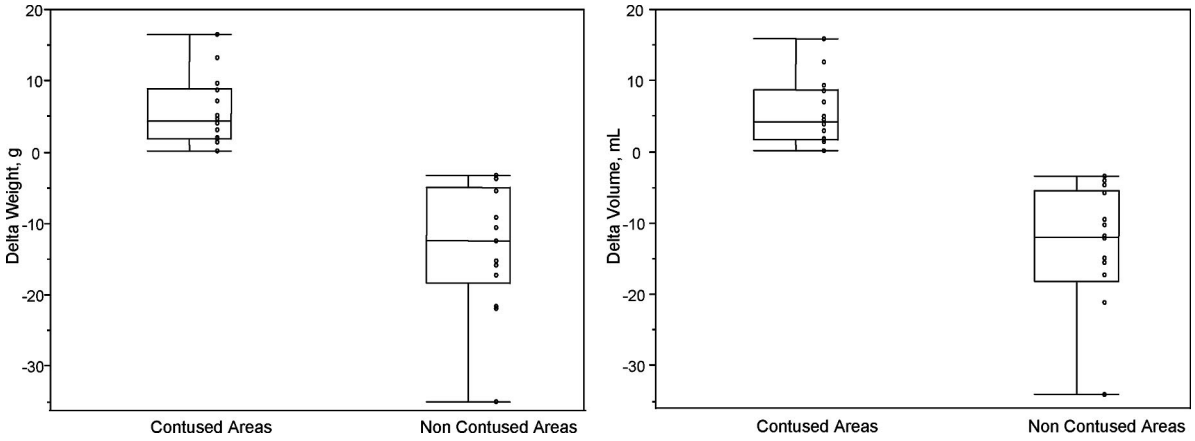

Figure 2. Mean effect of hypertonic saline on the weight and volume of contused and noncontused areas. The box plots summarize the distribution of points at each factor level. The ends of the box are the 25th and 75th quartiles. The line across the middle of the box identifies the median sample value. The whiskers extend from the ends of the box to the outermost data point that falls within the distances computed.

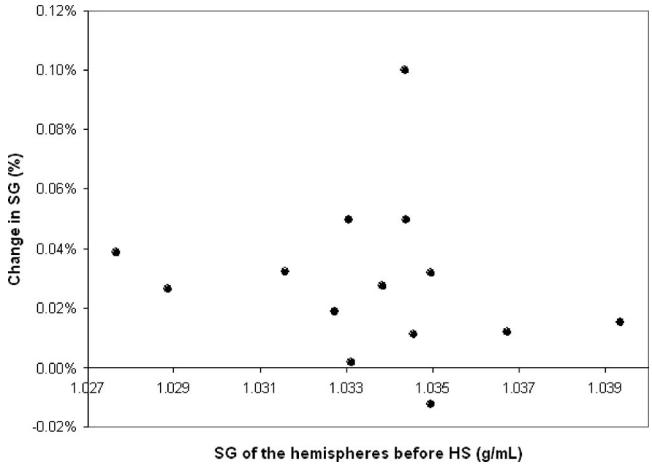

Figure 3. Change in specific gravity (*SG*) of the noncontused hemispheric areas induced by hypertonic saline (*HS*) according to baseline specific gravity.

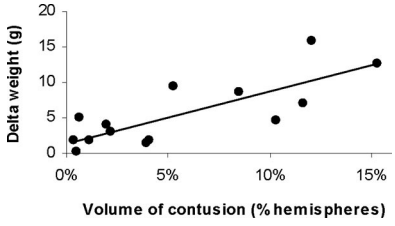

Figure 4. Change in the weight of contusion according to their initial volume assessed in percentage of the hemispheres.

initial opening is still partly unknown. Clearly, one has to consider the noncontused and the contused areas differently in this respect.

Regarding the noncontused areas, our data suggest that BBB permeability is unequally affected among patients since we observed a wide variability in response to hypertonic saline infusion in terms of SG change in these areas. As a mean, patients with TBI increased their SG in these areas after HS administration indicating an efficient BBB. We were not able to show differences in terms of age, initial Glasgow Coma Scale score, initial Simplified Acute Physiology Score II, mechanism of accident, delay between trauma and CT, mechanism of TBI, initial SG, and ICP between responders and nonresponders to HS. These results are coherent with most of the magnetic resonance imaging data available in experimental and human TBI showing that BBB is functional in the noncontused areas (18, 20, 21). However, one should acknowledge that the molecule used to test the BBB permeability might, by itself, affect the results. A passage through the BBB of large molecules such as gadolinium, gadolinium-DTPA (Gd-DTPA), or iodine might occur only in case of extensive damage. On the other hand, a slight change in BBB permeability could be evidenced only through the use of a small molecule such as salt. In this respect, we think that our study design gave us a unique opportunity to test the BBB permeability in human. In this context, the increase in SG that we observed after salt administration indicates that BBB is acting as a semipermeable membrane. Such a result was also observed by Saltarini et al. (22) in a patient with refractory intracranial hypertension using magnetic resonance imaging to assess cerebral water content. It is noteworthy that our measurements could be slightly biased by the fact that HS increases cerebral blood flow through a reduction in blood viscosity (23). When autoregulation is preserved, this increase in cerebral blood flow is combined with a decrease in cerebral blood volume that could slightly underestimate the effect of HS on SG since blood has a higher SG than brain tissue.

Regarding the contused areas, experimental data suggest that BBB remains open for a prolonged period of time after trauma. Our data suggest that this is true in human TBI, since HS consistently increased the weight and volume of contused areas. In the experiment by Tanno et al. (19), at 24 hrs after injury, abnormal permeability was restricted to the impact site and this area remained permeable up to 72 hrs after trauma. In ten patients with cerebral contusions 1–2 days after trauma, Kushi et al. (24) observed that contusion edema areas were frequently enhanced by Gd-DTPA indicating that an increased cerebrovascular permeability occurs early after trauma and suggesting that contusion edema may be at least partially vasogenic in nature. There are numerous arguments showing that the state of the BBB in the

contusion area might be very different in its time course than in noncontused areas. Experimentally, Beaumont et al. (25) demonstrated using an intravenous bolus of 0.2 mmol/kg Gd-DTPA with serial T1 MR images that BBB permeability was greatest in the site of contusion. Gd-DTPA accumulation was greatly enhanced by secondary insult such as hypoxia and hypotension. Bradykinin and arachidonic acid have been suspected as mediators of this secondary opening (26).

The maximum effect of HS has been consistently observed 20–25 mins following the end of bolus infusion. The mean duration of action has been reported at 93 mins (3). In the present study, we chose to perform the second CT right after the end of the bolus injection. This timing was chosen to reduce a potential time confounding effect and to avoid the displacement of the patient from the CT table, allowing us to maintain the head in the exact same position between the two CTs. Because of this timing, it is possible that we did not evaluate the effect of HS at its peak but slightly before. Nevertheless, this could change the absolute values that we measured but not the trends that we observed. Regarding natremia change, our measures were very closed to the one observed by Horn et al. (4). In their study, plasma Na^+ concentration increased from 141 ± 6 mmol/L to 143 ± 5 mmol/L 1 hr after 2 mL/kg of body weight 7.5% HS.

CONCLUSION

HS consistently increased the volume of contusion, whereas its effect on noncontused areas, although significant when taking all the patients together, showed marked interindividual variations.

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