JOURNAL OF SURGICAL RESEARCH 43, 37–44 (1987)

Hypertonic Saline Resuscitates Dogs in Endotoxin Shock[1]

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Presented at the Annual Meeting of the Association for Academic Surgery, Washington, D.C., November 5–8, 1986

In this experiment we determined if infusions of hypertonic saline (HS, 1080 Na meq/liter) could resuscitate dogs in endotoxin shock as effectively as Ringer's lactate (RL, 130 Na meq/liter). Anesthetized dogs received iv 0.5 mg/kg of *Escherichia coli* endotoxin, and mean arterial pressure (MAP, mm Hg) decreased from 148 ± 5 to 58 ± 14 within 30 min. To resuscitate the dogs 13 meq/kg of sodium was intravenously infused over 90 min as either a 10% body weight load of RL ($n = 5$) or a 1.2% body weight load of HS ($n = 5$). Both solutions produced an equivalent hemodynamic resuscitation 3 to 4 hr postinfusion with an increase in MAP (RL, 119 ± 4; HS, 108 ± 7), the restoration of cardiac outputs to baseline (RL, 2.0 ± 0.2; HS, 1.9 ± 0.3 liter/min), and similar renal inulin clearances (RL, 48 ± 16; HS, 44 ± 7 ml/min). The net fluid gain (resuscitation fluid volume infused minus urine output as percentage of body weight) was much greater in the RL group (7.2 ± 1.0%) than in the HS group (0.48 ± 0.2%). Plasma volume (PV, percentage of body weight) was measured with Evans blue dye in these splenectomized dogs. The increase in PV in the RL dogs (1.25 ± 0.04%) was slightly greater than the increase in the HS group (0.94 ± 0.13). Prenodal skin lymph was collected from both hindpaws, and the fractional increase in skin lymph flow after RL (4.5 ± 2.9) was greater than the increase in the HS group (1.7 ± 0.3). A small volume of HS can resuscitate dogs in endotoxin shock as well as an equal sodium load of RL by expanding the plasma volume with fluid that shifts to the intravascular compartment.

INTRODUCTION

Hypertonic saline solutions have been used to resuscitate patients in hemorrhagic shock, patients who are undergoing major surgery or who have been burned [1]. In experimental studies of resuscitation from shock, when equal sodium loads were administered the smaller volumes of hypertonic saline were as effective as the larger volumes of isotonic solutions [2–4]. Resuscitation of patients who are septic often requires large volumes of balanced electrolyte solutions which produce edema. It is not clear whether hypertonic saline has a role to play in the treatment of septic patients. The purpose of this study was to determine if hypertonic saline could reverse the adverse consequences of a substantial dose of endotoxin in anesthetized dogs as effectively as does Ringer's lactate.

METHODS

Male mongrel dogs, weighing 20 to 33 kg, anesthetized with intravenous sodium pentobarbital were splenectomized using sterile technique. Flunixin meglumine (Schering) was given postoperatively for analgesia for 5 days. More than 3 weeks after the splenectomy, the dogs were again anesthetized with intravenous sodium pentobarbitol (30 mg/kg). Supplemental pentobarbital doses were given as required to maintain anesthesia in these intubated, spontaneously ventilating animals. A right carotid artery catheter and a flow-directed pulmonary artery catheter were inserted, and these were used to measure pressures and thermodilution cardiac outputs (Edwards Laboratory Cardiac Output Computer) and for aspiration of blood samples. Systemic arterial and pulmonary artery pressures were recorded continuously on a polygraph. After a double lumen

[1] Sponsored by a grant from the Merit Review Board of the Veterans Administration.

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0022-4804/87 $1.50

catheter was inserted into the bladder through a short laparotomy incision the dogs were turned prone.

The lymphatics that drain paw skin and subcutaneous tissue were cannulated in both hindpaws of each dog. These lymphatics are located inferior to the popliteal lymph node and lie parallel to the lateral saphenous vein. The lymphatics located on both sides of the vein were ligated, with the largest one cannulated retrograde to the direction of flow with a heparin filled Silastic catheter. To facilitate lymph flow, the hindpaws were connected to an electric motor that flexed and extended the paws 30 times per minute. Lymph was collected in tared vials which contained 10 μl of a heparin solution (1000 units/ml). The change in weight of the vial divided by the length of time of collection gave the lymph flow rate (microliters per minute). Plasma was separated from a 5-ml heparinized arterial blood sample aspirated at the midpoint of the lymph collection period, which varied in duration from 15 to 30 min. A steady-state lymph flow was defined as two consecutive lymph flows within 20% of each other.

Ten dogs were studied. When lymph and urine flows were steady, baseline data were collected which included lymph samples, three or more serial urine collections to measure renal function, and a determination of plasma volume. Each dog then received 0.5 mg/kg of endotoxin (lipopolysaccharide W, *E. coli* 055:B5, Difco Laboratories) intravenously over 20 min. Ninety minutes after injection of the endotoxin, the dogs were randomly assigned to receive 13 meq Na/kg as either 100 cc/kg of Ringer's lactate (130 meq Na/liter) or 12 cc/kg of a hypertonic saline solution (1080 meq Na/liter). The resuscitation fluid was infused over 90 min. Most dogs developed tachypnea and received supplemental oxygen. Three to four hours after the infusion, when lymph and urine flows were steady, final postresuscitation data were collected. This final data included lymph flow, three or more serial urine collections, and a repeat measurement of plasma volume. The dogs were killed by the intravenous infusion of T-61 Euthanasia Solution (National Laboratories Corp.).

Total protein concentrations in plasma and lymph were determined using the method of Lowry *et al.* [5]. The lymph over plasma total protein concentration ratio (L/P) was calculated by dividing the lymph by the plasma concentration. The concentration of albumin in plasma was measured using immunoelectrophoresis [6]. Plasma volume was determined by regression analysis of six serial Evans blue plasma concentrations measured in samples collected during the 80 min following intravenous injection of 7 to 10 ml of 0.5% Evans blue dye. From the plasma concentration at the time of dye injection, which was predicted from the linear regression, we subtracted background Evans blue concentration measured in a sample collected immediately before injection. This corrected concentration was divided by the amount of Evans blue injected to determine the plasma volume. Evans blue concentration in diluted plasma was measured at 605 Å with a spectrophotometer.

At the completion of the experiment, duplicate 1- to 2-g tissue samples were collected. Skin and subcutaneous tissue were excised from the lateral region of the hindpaw and calf. Skeletal muscle tissue was excised from the gastrocnemius muscle. The antimesenteric side of the proximal small bowel was excised. Duplicate tissue samples were placed individually in tared glass vials. After the closed vials were reweighed, the reopened vials were placed in an oven at 60°C. The tissue samples were dried for at least 3 weeks until two consecutive weights were found to be within 5% of each other. The average wet over dry tissue weight ratio (W/D) was then determined.

After intravenous injection of a loading dose of inulin and PAH, a constant infusion was administered to maintain steady plasma inulin and PAH concentrations. Urine samples were collected over 30 min with plasma samples obtained at the midpoint. At the completion of each collection period the bladder was irrigated with distilled water and then flushed with air. At least three serial

30-min collections were performed during the baseline and final periods and an average clearance was determined. The plasma and urine inulin concentrations were measured with a β-indoleacetic acid reagent [7]. The PAH concentrations were measured with *N*-(1-napthyl)ethylenediamine [8]. The inulin clearance, the effective renal blood flow, and the osmolar clearance were calculated as outlined by Homer Smith [8]. Clearances and urine output are reported as milliliters per minute. The osmolalities of plasma and urine samples were measured by determining the freezing point depression with an osmometer.

Data are presented as the means plus or minus the standard error. The serial changes in the hemodynamic data were tested with a two-way analysis of variance, and when the *F* test was significant, the individual values were tested with a paired *t* test using Bonferonni correction of the *t* value for multiple comparisons [9]. A *P* value less than 0.05 was accepted as significant. Within the RL or HS groups the initial and final values for renal functions, hematocrit, plasma protein, lymph flow, lymph protein concentrations, and plasma volume were compared with a paired *t* test. Between the RL and HS groups the change calculated as the final value minus the initial value of plasma volume, total protein plasma concentration, urine flow rate, free water clearance, fractional lymph flow, *L/P*, and hematocrit were compared with an unpaired *t* test. *W/D* data of the HS group were compared to *W/D* data of the RL group with an unpaired *t* test.

RESULTS

Hemodynamic data. Both groups of dogs had similar baseline mean arterial blood pressures, which decreased by more than 50% after infusion of the 0.5 mg/kg of endotoxin. The dogs remained hypotensive until the fluid infusion was begun. The increase in blood pressure of the Ringer's lactate group was not significantly greater than the increase in the hypertonic saline group. The final mean arterial pressure was lower than the baseline mean arterial pressure (Fig. 1).

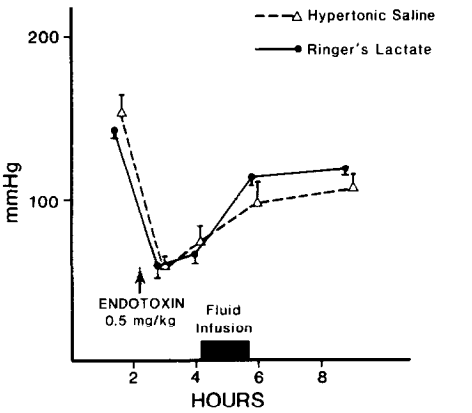

FIG. 1. The mean arterial pressures in the RL and HS groups are shown for five selected periods throughout the experiment: the initial baseline period, the period after intravenous injection of 0.5 mg/kg of endotoxin, the period before infusion of the resuscitation fluid, the period at the completion of the fluid infusion and the final period 3 to 4 hr following the end of the infusion. The final mean arterial pressures in both the RL and HS groups were lower than the baseline pressures.

The systemic arterial hypotension, caused by the endotoxin, was associated in every case with a fall in cardiac output, but there was no consistent change in either the pulmonary artery diastolic pressure or the pulmonary capillary wedge pressure. Following infusion of the resuscitation fluids the increase in mean cardiac output was similar in both the RL and HS groups. In neither group was the final mean pulmonary artery pressures or the final mean pulmonary artery wedge pressures different from their baseline value (Table 1).

Plasma volume and protein content. Infusion of Ringer's lactate equal to 10% of each dog's weight increased the mean plasma volume from 1080 ± 160 to 1412 ± 189 ml. Infusion of hypertonic saline equal to 1.2% of each dog's weight increased mean plasma volume from 868 ± 64 to 1113 ± 58 ml. In the 6.5 to 7.5-hr period from the administration of the endotoxin to the end of the experiment, mean total urine output in the dogs given RL was 784 ± 210 ml. In the 6.5 to 7-hr period from the administration of the endotoxin to the end of the experiment, 202

TABLE I

HEMODYNAMIC DATA

		Initial	Hypotension	Final
Cardiac output (liter/min)	RL	1.8 ± 0.3	1.2 ± 0.2	2.0 ± 0.2*
	HS	1.6 ± 0.2	1.2 ± 0.2	1.9 ± 0.3*
Pulmonary artery pressure (mm Hg)	RL	26 ± 2	18 ± 2	24 ± 2
Systolic		19 ± 2	14 ± 2	18 ± 2
Diastolic	HS	24 ± 4	21 ± 2	21 ± 2
		17 ± 2	16 ± 1	16 ± 2
Wedge pressure (mm Hg)	RL	13 ± 2	12 ± 1	15 ± 2
	HS	12 ± 2	11 ± 2	13 ± 2

* $P < 0.05$, different from preceding value.

± 36 ml of urine was collected from the HS group. The infused volume minus the urine output was used to calculate the net volume gain which was 18 times greater in the RL group than that in the HS group (Fig. 2). When the plasma volumes were calculated as the percentage of body weight, the increase of 1.25 ± 0.04% in the mean plasma volume of the RL group from the baseline mean value of 4.02 ± 0.25% was greater than the 0.94 ± 0.13 increase in the HS group from the baseline mean plasma volume of 3.34 ± 0.25% (Fig. 2). The increase in plasma volume was associated with a dilution of the plasma total protein concentration and a decrease in the hematocrit. The 27% decrease in the plasma total protein concentration of the RL group exceeded the 21% decrease in the HS group. The decreases in hematocrit were not significantly different (RL, 18 ± 3%; HS, 20 ± 2%) (Table 2). The dogs infused with HS had an increase in plasma osmolality (Fig. 3).

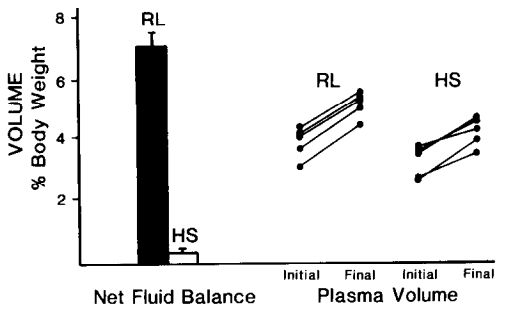

FIG. 2. The volume presented on the ordinate is normalized as the percentage of the dogs' body weights. The net fluid balance is the volume of resuscitation fluid infused minus the total volume of urine excreted after injection of the endotoxin. The net fluid balance in the RL group, represented as a solid bar, exceeded that of the HS group. The initial and final plasma volumes measured with Evans blue dye are presented on the left.

Renal function. Urine flow increased after resuscitation with both RL and HS, but the mean 10-fold increase in the urine flow rate in the RL group exceeded the 3-fold increase in the HS group (Table 3). The difference in postresuscitation diuresis was due in part to a greater rise in the free water clearance of the RL group, which had a mean increase of 1.8 ± 0.4 ml/min. The HS group had a mean increase in free water clearance of 0.7 ± 0.3 ml/min. In nine of the ten dogs, the final inulin clearance was less than the initial clearance. When the initial and final data were analyzed, there was a positive correlation between the mean arterial pressure and the inulin clearance ($R^2 = 0.335$, $P = 0.007$).

The effective renal blood flow, measured as PAH clearance and corrected for hematocrit, was normalized as a fraction of the cardiac output measured with thermodilution techniques. After resuscitation with RL there was a fall in the fractional renal blood flow from 26 ± 5 to 15 ± 2% of cardiac output.

TABLE 2

CHANGES IN INTERVASCULAR PARAMETERS FOLLOWING RESUSCITATION

	Protein concentration (mg/ml)		Plasma protein mass (g)	
	Initial	Final	Initial	Final
Ringer's lactate				
Total protein	60.4 ± 4.1	43.7 ± 2.9*	64.7 ± 9.0	61.6 ± 8.5
Albumin	28.2 ± 1.0	21.5 ± 1.4*	30.8 ± 5.3	31.0 ± 5.9
HCT	46.6 ± 0.7	37.1 ± 0.9*		
Hypertonic saline				
Total protein	61.1 ± 3.1	48.2 ± 2.7*	52.8 ± 3.6	53.6 ± 3.9
Albumin	26.9 ± 2.2	21.2 ± 2.2*	23.5 ± 3.0	23.6 ± 2.9
HCT	47.4 ± 3.1	38.9 ± 2.7*		

* $P < 0.05$, different from initial value.

After resuscitation with HS there was a fall in the fractional renal blood flow from 28 ± 6 to 16 ± 3% of cardiac output.

Lymph data. After resuscitation the mean skin lymph flow from the hindpaws significantly increased (Table 4). The fractional increase in the lymph flow was calculated as the final lymph flow minus the initial lymph flow divided by the initial lymph flow. The mean fractional increase in lymph flow from the RL hindpaws (4.5 ± 3.0, range: 1.3 to 20.8) was greater than the mean fractional increase in lymph flow from the HS hindpaws (1.7 ± 0.35, range: 0.82 to 3.3). With the increase in lymph flow there was a fall in the mean lymph protein concentration (Table 4). However, with dilution of the plasma total protein concentration, there was a significant decrease in the lymph over plasma total protein concentration ratio in the RL group (initial, 0.24 ± 0.04; final, 0.19 ± 0.03), but not in the HS group (initial, 0.26 ± 0.05; final, 0.25 ± 0.06) (Fig. 4).

The mean wet over dry tissue weight ratios of skin from the hindpaw and from the calf of the RL and HS groups were not significantly different (Table 5). However, the wet over dry tissue weight ratios of the gastrocnemius skeletal muscle and the jejunum were greater in the dogs resuscitated with RL.

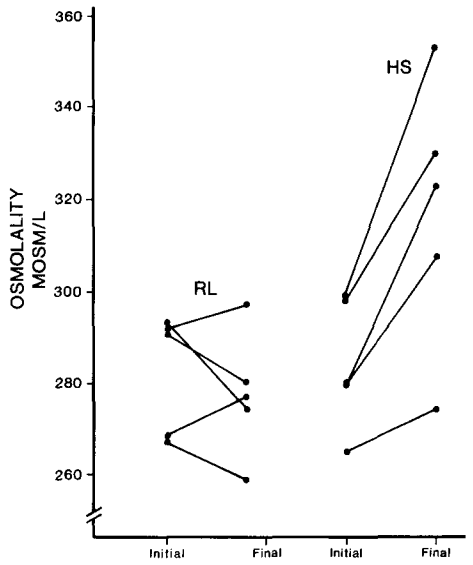

FIG. 3. The plasma osmolalities of blood samples collected during the initial baseline periods and the final periods are presented, and data from each dog are linked. Data on the left are from dogs infused with Ringer's lactate, and data on the right are from dogs infused with hypertonic saline.

DISCUSSION

Previous investigators have shown that small volumes of hypertonic saline can resuscitate dogs in hemorrhagic shock, but the role of hypertonic saline solutions in resuscitation of septic or endotoxic shock is less clear [10]. In this experiment 13 meq of sodium/kg of body wt, whether administered as an isotonic or a hypertonic solution, re-

TABLE 3

RENAL FUNCTION

		Initial	Final
Urine flow (ml/min)	RL	0.2 ± 0.1	2.2 ± 0.6*
	HS	0.2 ± 0.1	0.7 ± 0.1*
GFR (ml/min)	RL	63 ± 7	48 ± 16
	HS	69 ± 5	44 ± 7*
Free water clearance (ml/min)	RL	−1.2 ± 0.2	0.6 ± 0.4*
	HS	−1.1 ± 0.1	−0.4 ± 0.2

* $P < 0.05$, different from initial value.

versed hypotension in dogs that had been induced by *Escherichia coli* endotoxin. After resuscitation the cardiac outputs returned to baseline values, but the mean arterial pressures were lower than they were during the baseline period, indicating that there were decreases in peripheral resistance. Previous investigators have shown that unresuscitated dogs in endotoxin shock have a sustained increase in total peripheral resistance [11]. The results of this study suggest that the resuscitation of dogs in endotoxin shock by the intravenous infusion of sodium chloride-containing fluids is required to produce a "hyperdynamic" picture similar to that observed in septic patients [12]. Infusion of the resuscitation fluid increased the blood volume, but the pulmonary artery diastolic and the wedge pressures were not increased. These hemodynamic patterns are consistent with vasodilation in the venous capacitance and precapillary resistance vessels [13].

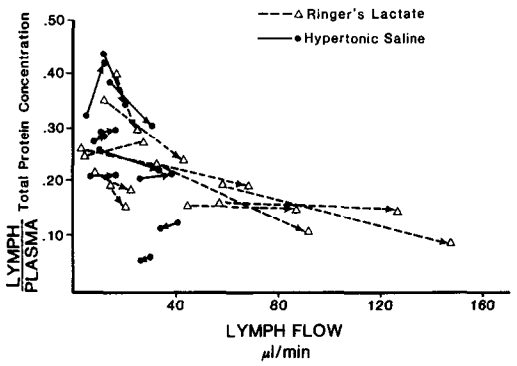

FIG. 4. The data from 20 hindpaws of 10 dogs are presented. The lymph flow rate is on the abscissa, and the lymph protein concentration, normalized as the lymph over plasma protein concentration ratio, is on the ordinate. The initial and final lymph flow rates are linked by arrows which show that skin lymph flow of the dogs infused with RL consistently increased, while the lymph flow response in the HS group is variable. The decrease in L/P with the increase in lymph flow suggests that the minimal, or filtration independent, L/P will be around 0.1

The reversal of endotoxin shock occurred when the plasma volume was expanded 25%. The plasma volume increase was one-seventh of the net positive fluid balance after infusion of Ringer's lactate. Some of the retained resuscitation fluid which is not in the plasma volume will be interstitial fluid or free fluid in the pleural or peritoneal cavities [14]. In contrast, after the hypertonic saline fluid infusion, the plasma volume expanded twofold more than the calculated net positive fluid balance. Therefore, one-half of the fluid which expands the plasma compartment after HS may have shifted from the intracellular compartment in response to the increase in extracellular fluid osmolality. The lower W/D in the skeletal muscle and small bowel tissues after HS resuscitation than that after RL resuscitation may reflect the shift of cell water out of these tissues.

Increases in lymph flow from skin tissues do not indicate that an increase in skin microvascular membrane permeability was produced by the endotoxin. We conclude that there is no evidence of a "capillary leak"

TABLE 4

LYMPH DATA

		Initial	Final
Lymph flow (μl/min)	RL	25.9 ± 10.6	66.6 ± 22.8*
	HS	17.7 ± 6.1	25.4 ± 5.0*
Lymph protein concentration (mg/ml)	RL	14.6 ± 2.5	8.2 ± 1.5*
	HS	15.8 ± 3.7	11.7 ± 2.3*

* $P < 0.05$, different from initial value.

after resuscitation with either RL or HS because with the increase in lymph flow, particularly for the RL group, there was a fall in the lymph over plasma total protein concentration ratio (L/P). A technique of permeability analysis developed by Taylor and Granger for use in lymph collection experiments consists of manipulating the Starling forces to increase lymph flow until a "filtration independent" L/P is achieved. Filtration independent means further increases in lymph flow are not associated with a further fall in L/P. The lower the filtration independent L/P the less permeable is the microvascular membrane to protein [15]. Figure 4 shows that the increase in lymph flow after RL, in the cases where the flow rates have increased two- to threefold, dropped the L/P toward a minimal value of 0.1. This low value of L/P is the same as the minimal values for L/P of total protein previously reported in studies of normal canine hindpaw skin lymph [15, 16]. Furthermore, in previous experiments where venous hypertension was used to increase lymph flow, we have shown that following resuscitation from endotoxin shock there is no increase in the skin microvascular permeability for proteins [16]. The increase in plasma volume, after the RL and the HS, diluted the HCT and the plasma total protein concentration. The plasma protein mass, calculated as concentration times plasma volume, did not decrease for either total protein or albumin. In the present experiment, the changes in plasma protein mass do not indicate that a shift of intravascular proteins to the interstitium has occurred, which is further evidence that after resuscitation from endotoxin shock microvascular membrane permeability had not changed.

TABLE 5

WET OVER DRY TISSUE WEIGHT RATIO

	HS	RL
Hindpaw skin	3.26 ± 0.15	3.54 ± 0.25
Calf skin	3.52 ± 0.31	3.68 ± 0.22
Gastrocnemius	4.05 ± 0.12	4.72 ± 0.41*
Jejunum	4.30 ± 0.20	5.04 ± 0.23*

* $P < 0.05$, different from HS.

Despite a similar final mean arterial pressure, there was a greater increase in skin and subcutaneous tissue lymph flows after RL resuscitation. The greater increase in lymph flow cannot be attributed to the slightly greater dilution in plasma total protein concentration after RL. The smaller increase in skin lymph flow after HS may reflect greater cutaneous vasoconstriction due to an increase in circulating sympathetic catecholamines and vasopressin. These potent vasoconstrictors shift the flow of blood away from the cutaneous microcirculation, reducing surface area and microvascular hydrostatic pressure. Previous investigators have reported that when a hypertonic saline resuscitation increases the plasma osmolality more than 10 mosm there is an increase in vasopressin and circulating catecholamines [17].

After resuscitation the glomerular filtration rate (GFR) decreased in 9 of the 10 dogs. This fall in GFR may have occurred because the

postresuscitation mean arterial pressure was lower as suggested by the positive correlation between GFR and MAP. However, in addition, the effective renal blood flow (ERBF), measured with PAH, indicates that after resuscitation there was a shift of cardiac output away from the renal circulation. During the baseline period the ERBF was 19 to 36% of the cardiac output. After resuscitation the renal blood flow was 7 to 21% of the cardiac output. Vasoconstriction factors released from the kidney may have been responsible for the decrease in renal blood flow. While the decrease from initial to final values of GFR and RBF were similar to those in the RL and HS groups, there was a significantly greater increase in the urine output of the RL group after resuscitation (Table 3). The greater urine flow in the RL group was the consequence of a higher free water clearance (FWC). As the absorption of filtrate fluid by the collecting tubule increases, the urine becomes more concentrated and the FWC lowers [8]. The smaller increase in the FWC after resuscitation in the HS group, despite a similar increase in plasma volume in both the RL and HS groups, is consistent with a higher circulating vasopressin level after HS resuscitation.

In conclusion HS can reverse hypotension in dogs in endotoxin shock with a smaller infusion volume than is required for a RL resuscitation. The shift of fluid out of the intracellular compartment of skeletal muscle and small bowel in response to the increase in extracellular osmolality after HS appears to contribute to the increase in blood volume. However, an increase in cutaneous arteriolar resistance after HS greater than that after RL infusion may also contribute to the reversal of hypotension. An increase in vasopressin after HS may reduce the postresuscitation diuresis by increasing water reabsorption from the tubules.

REFERENCES

1. Monafo, W. W., Chuntrasakul, C., and Ayvazian, V. H. Hypertonic sodium solutions in the treatment of burn shock. *Am. J. Surg.* **126:** 778, 1973.
2. Kramer, G. C., Perron, P. R., Lindsey, D. C., Ho, H. S., Gunther, R. A., Boyle, W. A., and Holcroft, J. W. Small-volume resuscitation with hypertonic saline dextran solution. *Surgery* **100:** 239, 1986.
3. Nakayama, S., Kramer, G. C., Carlsen, R. C., and Holcroft, J. W. Infusion of very hypertonic saline to bled rats: Membrane potentials and fluid shifts. *J. Surg. Res.* **38:** 180, 1985.
4. Shackford, S. R., Sise, M. J., Fridlund, P. H., *et al.* Hypertonic sodium lactate versus lactate Ringer's solution for intravenous fluid therapy in operations on the abdominal aorta. *Surgery* **94:** 41, 1983.
5. Lowry, O. H., Rosebrough, N. J., Farr, P. L., and Randall, R. S. Protein measurement with the Folin phenol reagent. *J. Biol. Chem.* **193:** 265, 1951.
6. Laurell, C. B. Electroimmunoassay. *Scand. J. Clin. Lab. Invest.* **29**(Suppl. 124): 21, 1972.
7. Heyrovsky, A. A new method for the determination of inulin in plasma and urine. *Clin. Chim. Acta* **1:** 470, 1956.
8. Smith, H. W. *Principles of Renal Physiology.* New York: Oxford Univ. Press, 1956.
9. Wallenstein, S., Zucker, C. I., and Fleiss, J. L. Some statistical methods useful in circulation research. *Circ. Res.* **47:** 1, 1980.
10. Velasco, I. T., Pontieri, V., Rocha E Silva, M., and Lopes, O. U. Hyperosmotic NaCl and severe hemorrhagic shock. *Am. J. Physiol.* **239:** H664, 1980.
11. Chien, S., Chang, C., Dellenback, R. J., *et al.* Hemodynamic changes in endotoxin shock. *Am. J. Physiol.* **210:** 1401, 1966.
12. MacLean, L. D., Mulligan, W. G., McLean, A. P. H., *et al.* Patterns of septic shock in man—A detailed study of 56 patients. *Ann. Surg.* **160:** 543, 1967.
13. Rowe, G. G., McKenna, D. H., Corliss, R. J., and Sialer, S. Hemodynamic effects of hypertonic sodium chloride. *J. Appl. Physiol.* **32:** 182, 1972.
14. Mullins, R. J., and Bell, D. R. Changes in interstitial volume and masses of albumin and IgG in rabbit skin and skeletal muscle after saline volume loading. *Circ. Res.* **51:** 305, 1982.
15. Taylor, A. E., and Granger, D. N. Exchange of macromolecules across the microcirculation. *In* E. M. Renkin and C. C. Michel (Eds.), *Handbook of Physiology—The Cardiovascular System,* Washington, D.C.: Am. Physiol. Soc., 1984. P. 961.
16. Mullins, R. J., and Lenfesty, B. S. Skin microvascular permeability after resuscitation with Ringer's lactate from endotoxin shock. *Surg. Gynecol. Obstet.* **164:** 49, 1987.
17. Hasser, E. M., Haywood, J. R., and Bishop, V. S. Role of vasopressin and sympathetic nervous system during hypertonic NaCl infusion in conscious dogs. *Am. J. Physiol.* **248:** H652, 1985.