Fluid compartments in hemorrhaged rats after hyperosmotic crystalloid and hyperoncotic colloid resuscitation

PAULA F. MOON, MICHELE A. HOLLYFIELD-GILBERT, TAMARA L. MYERS, TATSUO UCHIDA, AND GEORGE C. KRAMER
Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, New York 14853; and Office of Biostatistics, Department of Anesthesiology and Physiology, University of Texas Medical Branch, Galveston, Texas 77550-2778

Moon, Paula F., Michele A. Hollyfield-Gilbert, Tamara L. Myers, Tatsuo Uchida, and George C. Kramer. Fluid compartments in hemorrhaged rats after hyperosmotic crystalloid and hyperoncotic colloid resuscitation. *Am. J. Physiol.* 270 (*Renal Fluid Electrolyte Physiol.* 39): F1–F8, 1996.—Postresuscitation organ failure may be associated with detrimental changes in body fluid compartments. We measured how shock and resuscitation acutely alters the interstitial, cellular, and plasma compartments in different organs. Nephrectomized, anesthetized rats were bled to 50 mmHg mean arterial pressure for 1 h, followed by 60 min of resuscitation to restore blood pressure using 0.9% normal saline (NS, $n = 10$), 7.5% hypertonic saline (HS, $n = 8$), 10% hyperoncotic albumin (HA, $n = 8$), or 7.5% hypertonic saline and 10% hyperoncotic albumin (HSA, $n = 7$). A 2-h ^{51}Cr-EDTA distribution space estimated extracellular fluid volume (ECFV), and a 5-min ^{125}I-labeled albumin distribution space measured plasma volume (PV). Total tissue water (TW) was measured from wet and dry weights; interstitial fluid volume (ISFV) and cell water were calculated. NS resuscitation required 7 times more fluid (50.9 ± 7.7 vs. 8.6 ± 0.7 for HA, 5.9 ± 0.4 for HS, and 3.9 ± 0.5 ml/kg for HSA), but there were no differences between solutions in whole animal PV, ECFV, or ISFV. Fluid shifts within tissues depended on resuscitation solution and type of tissue. TW was significantly reduced by hypertonic saline groups in heart, muscle, and liver ($P < 0.05$). ISFV was significantly reduced by HA groups in the skin. In all tissues, mean cell water in groups receiving HS was smaller; this was significant for heart, lung, muscle, and skin. In conclusion, *1*) HS solutions mobilize fluid from cells while expanding both PV and ISFV, and *2*) TW and cellular water increase with both isotonic crystalloids and hyperoncotic colloids in many tissues.

fluid therapy; hypertonic saline; cellular edema; interstitial edema; shock

HYPOVOLEMIC SHOCK INDUCES profound alterations in the body's fluid compartments. Extravascular fluid decreases during hypovolemia because of compensatory homeostatic mechanisms that translocate interstitial fluid into the circulation to maintain plasma volume (PV) (6). There is a further decrease in interstitial fluid as water moves into cells during shock because of altered membrane function (3, 18, 21, 22). One goal of fluid resuscitation is to reverse these abnormalities by improving perfusion and oxygen delivery to tissues. The optimal fluid, be it crystalloids or colloids, is still a controversial issue (26). Isotonic crystalloids have the advantage of replacement of the interstitial fluid deficit as well as PV expansion, since only 20–40% of the infused fluid remains within the vascular spaces. A disadvantage to crystalloids, however, is that large volumes are required to sustain PV, and this may overexpand the interstitial space and cause edema (1, 13). Colloid solutions have been suggested to be beneficial in preventing interstitial edema, particularly in the lungs, because the oncotic pressure of these solutions maintains the fluid intravascularly. On the other hand, it has been suggested that colloids may cause pulmonary edema if careful, intensive monitoring is not provided, limiting their usefulness in an emergency situation (26). To add further complexity to the discussion, hypertonic saline (HS) solutions are being used with increasing frequency. Clinical trials suggest small-volume hypertonic saline solutions produce a more rapid resuscitation from trauma and cause less fluid overload or edema than conventional therapy (2, 4, 20, 24).

Different resuscitation solutions may have vastly different effects on organ fluid compartments and ultimately postresuscitation organ function. It is clear that crystalloids expand the interstitial space to a greater degree than colloids, but there is almost no data on the relative effects of these solutions on cell volume. In addition, measurement of compartmental fluid shifts after HS has been studied primarily in theoretical models in which uniform cellular dehydration was assumed (14). Direct measurements of interstitial and cellular spaces of different organs after resuscitation with hypertonic saline solutions have not been studied.

The goal of this study was to measure the major fluid compartments of different tissues during the acute phase of fluid resuscitation from hemorrhagic shock. Specifically, a comparison was made in the postresuscitation fluid distributions after resuscitation from hemorrhage shock with 0.9% isotonic saline, 7.5% HS, 10% hyperoncotic albumin (HA), and a combination of 7.5% hypertonic saline and 10% hyperoncotic albumin (HSA).

MATERIALS AND METHODS

Animal instrumentation. The study was approved by the University of Texas Medical Branch Animal Care and Use Committee. Forty male albino Wistar rats, weighing ~275–350 g were anesthetized with 5 mg/100 g subcutaneous pentobarbital sodium (Abbott Laboratories, North Chicago, IL). A rectal temperature probe monitored body temperature, and a heating pad assisted in maintaining temperature at 38.5°C. The femoral artery and vein were cannulated with polyethylene tubing (Intramedic Nonradiopaque PE-50; Clay Adams, Becton-Dickinson, Parsippany, NJ) using a cut-down surgical technique. The venous cannula was used to infuse replacement fluids during instrumentation and baseline and to administer isotopes and resuscitative fluid during the experiment. The arterial cannula was used to monitor sys-

temic blood pressures and heart rate, as well as withdraw blood during hemorrhage and obtain blood samples for hematocrits, total protein, electrolytes, and radioactivity levels. Five percent bovine serum albumin (Sigma Chemical, St. Louis, MO) was administered to all animals at 0.6 $ml \cdot g^{-1} \cdot h^{-1}$ iv for replacement of fluid losses during surgery. All fluids were infused with a Harvard compact infusion pump (model 975; Harvard Instruments, South Natick, MA). After vessel cannulation, retroperitoneal bilateral renal vascular occlusion was performed to prevent renal filtration of the ^{51}Cr-EDTA. This technique was employed instead of a bilateral nephrectomy to decrease surgical time and therefore surgical stress to the rats. A longitudinal incision through each kidney and visualization of no blood flow ensured vascular occlusion.

Experimental protocol. After instrumentation, a 30-min baseline period was begun. Fifteen minutes into baseline, 40 μCi of ^{51}Cr-EDTA complex (New England Nuclear, Wilmington, DE) was administered intravenously over 1 min. After baseline, each rat was randomly assigned to one of four groups. All groups were subjected to a 60-min hemorrhagic shock phase and a 60-min resuscitation phase. The hemorrhagic shock phase began by withdrawal of 1–2 ml of blood over 10 min until a mean arterial pressure (MAP) of 50 mmHg was obtained. Subsequent blood was withdrawn or reinfused as needed to maintain this MAP for 60 min. During the resuscitation phase, rats received one of four test solutions in a "blinded" fashion. Solutions were prepared and placed in coded syringes by a technician not directly involved with the surgery or data collection. The normal saline (NS) group received 0.9% saline (288 mmol/kgH_2O, Baxter Healthcare, Deerfield, IL). The HA group received 10% human albumin (Alpha Therapeutic, Los Angeles, CA). The HS group received 7.5% HS (2,400 mmol/kgH_2O), and the HSA group received a solution of 7.5% HS/10% albumin. The test solution was initially infused at 1 $ml \cdot kg^{-1} \cdot min^{-1}$ iv for the first 4 min and then administered as needed to maintain target MAP for a total of 60-min resuscitation. The target MAP for resuscitation was equal to 80% of the average baseline MAP or 80 mmHg, whichever was higher. Five minutes prior to the end of resuscitation, 8 μCi of purified ^{125}I-labeled albumin complex (New England Nuclear) was infused as a marker to measure PV. Before use, ^{125}I-albumin was dialyzed against phosphate-buffered saline to reduce free iodine to <1%. A 3-ml blood sample was obtained immediately before the animal was killed within 1–2 breaths with an overdose of inhaled isoflurane (USP) applied to the nares (AErrane; Anaquest, Madison, WI). Isoflurane was used for killing the animal to eliminate any effects hypertonic intravenous solutions might have on tissue fluid compartments.

After death, rats were dissected within a humidified chamber, and ~0.5–1.0 g from each of the following tissues was obtained: ventral abdominal skin, lumbar back skin, medial hind limb skin, gastrocnemius muscle, diaphragm, left ventricle, right ventricle, right lower lung lobe, liver, stomach, jejunum, ileum, cerebrum, and cerebellum, and all peritoneal and chest fluid. Samples were promptly placed in tared tubes, covered to prevent evaporation, and weighed using a Mettler balance (model AE200; Mettler Instrument, Highstown, NJ).

Measured variables. Extracellular fluid volume (ECFV) was measured by the 2-h distribution of ^{51}Cr-EDTA. A preliminary study indicated that steady-state ^{51}Cr-EDTA levels in blood, muscle biopsies, and skin biopsies were reached within 1 h of tracer administration for both normovolemic rats and rats subjected to shock and isotonic crystalloid resuscitation; other organs reached equilibration in a shorter time period. This was in agreement with previous reports suggesting that a 2-h equilibration of ^{51}Cr-EDTA would adequately achieve steady-state levels in our study (10, 11).

Systemic MAP, systolic and diastolic blood pressures, and heart and respiratory rate were determined at 15-min intervals throughout the study from pressure tracings measured with a calibrated pressure transducer (Utah Medical, Midvale, UT) and displayed on a strip chart recorder (Gilson Medical, Middleton, WI). Blood hematocrits were taken at 15-min intervals throughout the study. Plasma from the final blood sample was used to measure final hematocrit, total protein, electrolytes (Lablyte System 810; Beckman, Brea, CA), and the serum radioactivity of the two isotopes.

The volume of blood collected during hemorrhage was recorded, and duplicate 1-ml aliquots were used for isotope counting. Duplicate 100-μl plasma samples were also taken from the end of shock sample and from the 30-min resuscitation sample and were diluted to a standard 1 ml volume for isotope counting. Weighed samples of each stock isotope solution were serially diluted, and duplicate 1-ml aliquots used to determine the infused dose for each isotope for each individual experiment. The infused volume of stock solution was determined by weighing the injection syringe before and after infusion. The tissues, hemorrhaged blood, plasma samples, isotope standards, and blanks were counted for 20 min each in a scintillation counter (Packard Auto-Gamma Scintillation Spectrometer; Packard Instrument, Downers Grove, IL) to determine ^{125}I and ^{51}Cr radioactivity levels. For each sample, corrections were made for background radioactivity and for ^{51}Cr crossover into the ^{125}I channel. For duplicate and triplicate samples, the average radioactivity of each isotope was used in the calculation of the fluid distributions. After counting, tissues were placed in an 85°C oven until consistent dry weights, to 0.0005 g, were obtained. With the measured wet and dry weights, total tissue water (TW) per dry weight was calculated for each tissue as follows

$$\text{TW in } \mu l/g = \frac{(\text{wet wt} - \text{dry wt})}{\text{dry wt}} \times 100$$

Fluid spaces were determined for the whole animal and in the tissues. Total body ECFV and PV were calculated as

$$\text{ECFV in ml/kg} = \frac{\text{dose } ^{51}\text{Cr (in cpm)}}{\text{plasma } ^{51}\text{Cr (in cpm} \cdot \text{ml}^{-1} \cdot \text{kg body wt}^{-1})}$$

$$\text{PV in ml/kg} = \frac{\text{dose } ^{125}\text{I (in cpm)}}{\text{plasma } ^{125}\text{I (in cpm} \cdot \text{ml}^{-1} \cdot \text{kg body wt}^{-1})}$$

A correction was made to the infused dose of ^{51}Cr by subtracting the total ^{51}Cr in counts per minute (cpm) removed in the hemorrhaged blood. The volume of ECFV lost during blood sampling for hematocrits was assumed to be negligible because of the small volume involved and because this volume was consistently removed from each animal in all groups. Interstitial fluid volume (ISFV) was calculated as

$$\text{ISFV in ml/kg} = \text{ECFV} - \text{PV}$$

Table 1. *Two-way layout of four test solutions*

	NS	HA	HS	HSA
Albumin	0.0	10.0	0.0	10.0
NaCl	0.9	0.9	7.5	7.5

Values are in percent. Solutions were administered for 1 h to anesthetized rats after hemorrhagic shock. NS, normal saline ($n = 10$); HA, hyperoncotic albumin ($n = 8$); HS, hypertonic saline ($n = 8$); HSA, hypertonic saline + hyperoncotic albumin ($n = 7$).

Tissue fluid distributions were calculated as

$$\text{ECFV in } \mu l/g = \frac{\text{tissue } ^{51}\text{Cr (in cpm/g)}}{\text{plasma } ^{51}\text{Cr (in cpm/ml)}} \times 1{,}000 \text{ (in } \mu l/ml)$$

$$\text{PV in } \mu l/g = \frac{\text{tissue } ^{125}\text{I (in cpm/g)}}{\text{plasma } ^{125}\text{I (in cpm/ml)}} \times 1{,}000 \text{ (} \mu l/ml)$$

$$\text{Cell water in } \mu l/g = \text{TW} - \text{tissue ECFV}$$

$$\text{ISFV in } \mu l/g = \text{tissue ECFV} - \text{tissue PV}$$

The tissue spaces were expressed in microliters per gram dry weight of tissue by multiplying the tissue volume by the ratio of wet weight to dry weight for that tissue. Because ^{51}Cr does not readily cross the blood-brain barrier, ECFV in the brain could not be measured, and ISFV and cell water were not calculated for brain.

Rats were included in the analysis only if they survived throughout the resuscitation phase and the plasma ^{51}Cr levels did not decrease >15% from the 30- to the 60-min shock times, indicating appropriate renal vascular occlusion.

Statistical analysis. Blood pressure, hematocrit, volume of blood removed, and volume of resuscitation fluid administered were analyzed as a three-factor factorial experiment with repeated measures on one of the factors, time. Analysis was done for blood pressure at baseline, end of shock, and 5, 10, 30, and 60 min into resuscitation; for hematocrit at baseline, end of shock, and 30 and 60 min into resuscitation; for total shed blood at the end of shock; and for total test solution given during resuscitation. The other two factors were defined by the type of fluid resuscitation as saline (NS or HS) and albumin (none or HA) (see Table 1). A "hypertonic saline effect" is defined as the difference between HS groups and isotonic groups. Similarly, a "hyperoncotic albumin effect" is defined as the difference of HA groups and nonalbumin groups.

Tissue data indicated no differences between the left or right ventricle, so the left ventricle was selected as the heart sample; between cerebrum or cerebellum, the cerebrum was selected as the brain sample; between fundus, jejunum, or ileum, the jejunum was selected for the gut sample; or between any of the skin samples, abdominal skin was selected as the skin sample for further statistical analysis. Results of fluid distribution measurements for the whole rat and for these selected tissues were analyzed as a two-factor factorial experiment for each response variable. The two factors were saline and albumin, as previously defined. All results are reported as means ± SE.

RESULTS

Thirty-three rats met criteria to be included in the study (Table 1). Seven rats were not included because ^{51}Cr levels did not meet steady-state criteria, as described previously, during the shock phase. There was no difference between groups during baseline or shock for any parameter. During shock, the mean blood removed from each group was not statistically different (19.1 ± 1.2 HA, 19.1 ± 1.9 HSA, 21.9 ± 1.8 HS, and 24.0 ± 2.2 ml/kg NS) and was about one-third of the calculated blood volume for a rat (Fig. 1). During NS resuscitation, approximately two times the shed blood volume was required to reach and maintain target MAP. This volume was almost seven times more fluid than the HS, HA, and HSA groups required during resuscitation. Furthermore, HS, HA, and HSA all required significantly less fluid for resuscitation than the volume of blood shed during shock (Fig. 1). Although there were no statistical differences between these three groups, there was a trend for HSA to require the least volume of fluid, followed by HS and then by HA (Fig. 1). The manner in which the fluid was administered was also different between groups. A constant infusion of NS was required to maintain target MAP, whereas the initial infusion of fluid achieved MAP in the other three groups and very little additional fluid was required (Fig. 2). Three of eight HS (38%), three of eight HA (38%), and four of seven HSA (57%) rats did

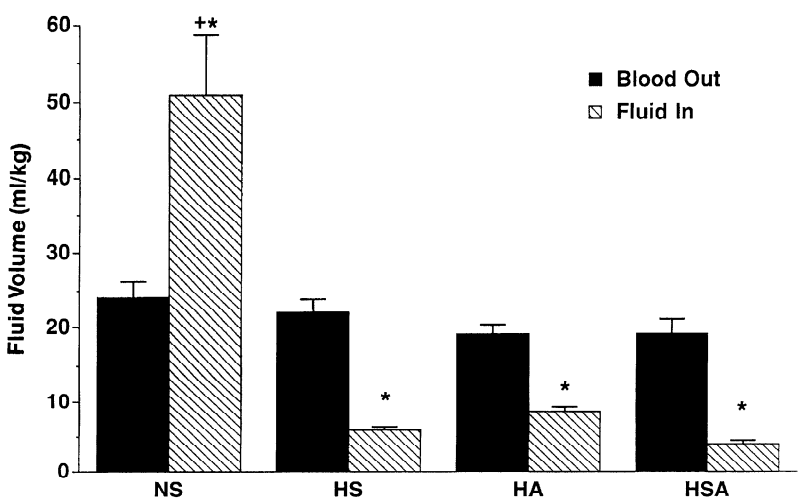

Fig. 1. Fluid balance for volume of blood removed and fluid administered (means ± SE) during hemorrhagic shock and resuscitation of anesthetized rats. Resuscitation was with 0.9% normal saline (NS), 7.5% hypertonic saline (HS), 10% hyperoncotic albumin (HA), or 7.5% hypertonic saline + 10% hyperoncotic albumin (HSA). *$P \leq 0.05$, significantly different from blood volume removed. +$P \leq 0.05$, volume of fluid infused is significantly different compared with other groups.

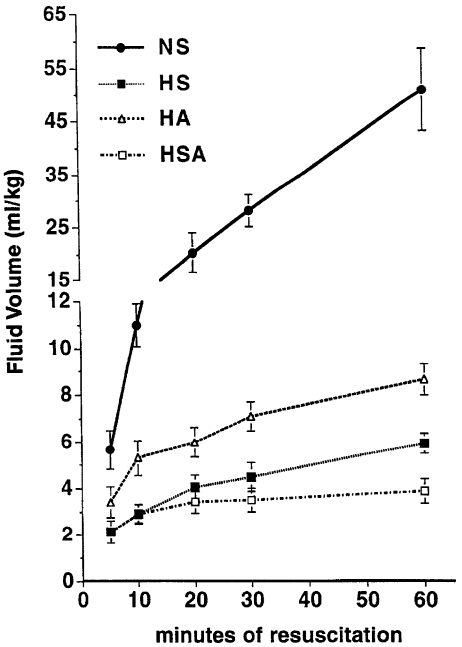

Fig. 2. Cumulative volume of resuscitation fluids (means ± SE) administered during 1-h resuscitation phase after 1 h of hemorrhagic shock in anesthetized rats. Abbreviations are as in Fig. 1.

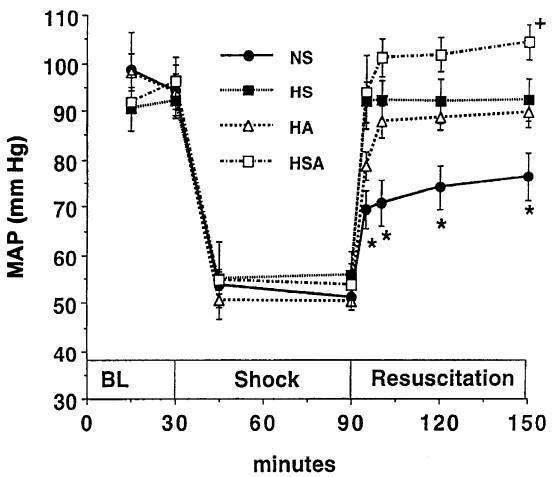

Fig. 3. Mean systemic arterial pressure (MAP, means ± SE) for baseline (BL), hemorrhagic shock, and resuscitation in anesthetized rats. Abbreviations are as in Fig. 1. *$P \leq 0.05$, NS significantly lower than all other groups, except at 95 min, when NS was significantly lower than only HSA and HA. +$P \leq 0.05$, HSA significantly higher than all other groups at 150 min.

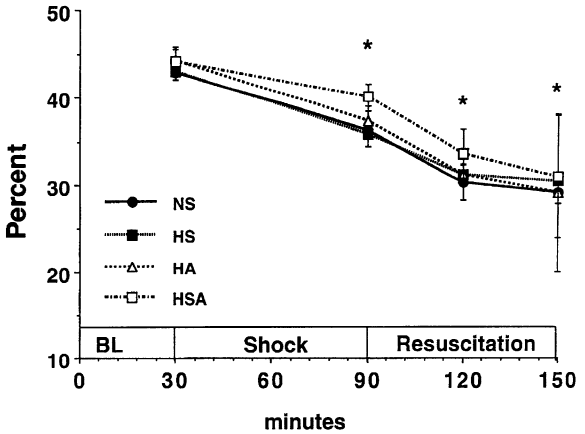

Fig. 4. Percent hematocrit (means ± SE) during baseline (BL), hemorrhagic shock, and resuscitation in anesthetized rats. Abbreviations are as in Fig. 1. *Significantly lower than baseline values for all groups but no significant difference between groups.

not require additional fluid after 20 min of resuscitation. Furthermore, three of the four HSA rats required no further fluid resuscitation after the initial bolus dose of HSA.

Blood pressure increased during resuscitation, as expected, based on experimental design, but differences were observed between groups (Fig. 3). The first few minutes of resuscitation appeared to be a critical hemodynamic transition period. After the initial infusion, at 5 min of resuscitation, all groups had reached target MAP, but both HS and HSA had significantly higher MAP than NS. HA was not significantly different from either NS or HS and HSA. After 10 min of resuscitation, blood pressure stabilized for each group. Although NS reached and maintained target MAP, MAP was significantly lower than the MAP for all other groups. HS and HA reached their baseline blood pressure after the initial 4 $ml \cdot kg^{-1} \cdot min^{-1}$ bolus infusion. This was 20% higher than target MAP, and these groups maintained this pressure throughout resuscitation. The MAP for HSA was higher than baseline for the entire resuscitation phase, and blood pressure was significantly higher than any other group after 60 min of resuscitation. Hematocrit significantly decreased at each time point throughout the study, but there was no difference between experimental groups (Fig. 4).

Final whole animal PV, ECFV, and ISFV, electrolytes, and total protein for all groups are provided in Table 2. There were no significant differences between groups for whole animal PV, ECFV, or ISFV (Fig. 5).

Table 2. *Fluid compartments and blood chemistries after 1 h of fluid resuscitation after hemorrhagic shock in anesthetized rats*

Group	PV, ml/kg	ECFV, ml/kg	ISFV, ml/kg	[Na], mmol/l	[K], mmol/l	[Cl], mmol/l	[TP], g/dl
NS	42.1 ± 4	310 ± 35	266 ± 32	144 ± 1.4	5.1 ± 0.3	117 ± 1.6	2.7 ± 0.2
HS	40.1 ± 3.4	294 ± 15	254 ± 15	149 ± 3.7	4.7 ± 0.2	125 ± 1.0	3.1 ± 0.1
HA	43.4 ± 5.3	285 ± 49	241 ± 50	143 ± 0.7	5.5 ± 0.5	113 ± 0.6	4.1 ± 0.2
HSA	34.0 ± 3.6	312 ± 31	278 ± 30	154 ± 2.9	5.5 ± 0.3	124 ± 3.4	3.7 ± 0.1

Values are means ± SE. Rats were resuscitated with amounts shown in Table 1; n is as in Table 1. PV, plasma volume; ECFV, extracellular fluid volume; ISFV, interstitial fluid volume; [Na], sodium concentration; [K], potassium concentration; [Cl], chloride concentration; [TP], total protein concentration.

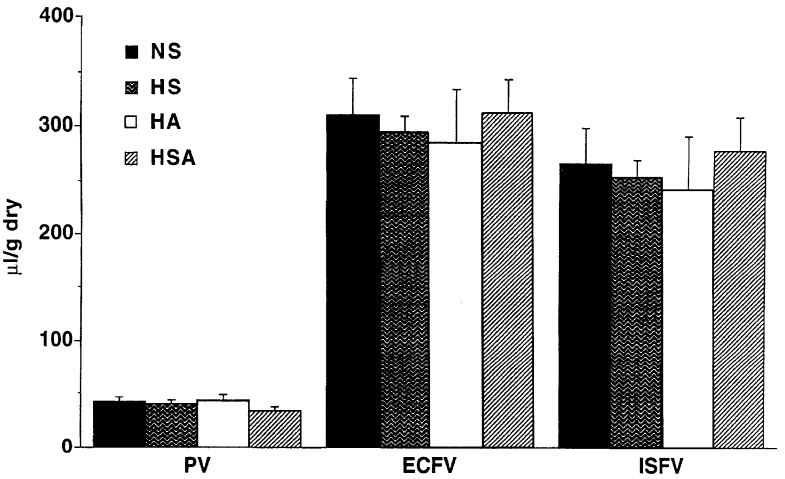

Fig. 5. Whole animal fluid compartments (means ± SE) of anesthetized rats after 1 h of hemorrhagic shock and 1 h of fluid resuscitation. PV, plasma volume; ECFV, extracellular fluid volume; ISFV, interstitial fluid volume; other abbreviations are in Fig. 1.

Groups receiving HS and HSA had elevated serum sodium and chloride concentrations, although statistical analyses were not done. Groups receiving HA and HSA maintained total protein concentrations, similar to baseline, whereas NS had a total protein concentration lower than any other group.

Figures 6–9 illustrate the final distributions of all tissue fluid compartments for all groups. There was significantly less TW in heart ($P = 0.022$), muscle ($P = 0.008$), and liver ($P = 0.047$) in HS and HSA groups (Fig. 6). A similar trend was seen in jejunum, diaphragm, and brain, although this was not statistically significant. The lung was the only tissue where, instead, there appeared to be less TW when resuscitated with albumin ($P = 0.052$). ISFV was not different between groups for any tissue except in the skin (Fig. 7). Skin ISFV ($P = 0.025$) was significantly smaller in the albumin groups (HA and HSA). Cell volume was significantly smaller in the heart ($P = 0.007$), lung ($P = 0.040$), muscle ($P = 0.021$), and skin ($P = 0.031$) of the HS groups, and a similar trend was observed in the other tissues (Fig. 8). The PV for all tissues was not different between groups except for the brain (Fig. 9). The HSA group had a smaller mean brain PV than the other groups (Table 2), but this difference was statistically significant only between HSA and HA ($P = 0.028$).

DISCUSSION

This study compared acute compartmental fluid shifts subsequent to hemorrhagic shock and resuscitation with different types of resuscitation fluid. All solutions restored MAP, and there was no difference between solutions in whole animal ISFV, ECFV, or PV. Results from the tissue data indicated a heterogeneity in fluid compartments between organs, as well as differences in tissue fluid compartments due to type of fluid used for resuscitation.

HSA animals received the smallest volume of resuscitation fluid, yet they achieved the highest MAP and reached it more quickly than any other group. NS animals were the slowest to achieve target MAP and required a near continuous infusion of the largest volume of fluid. Because there was equal PV expansion in all groups, other factors may have been responsible for the differences in blood pressures. HS has positive inotropic effects (7) and decreases afterload or systemic

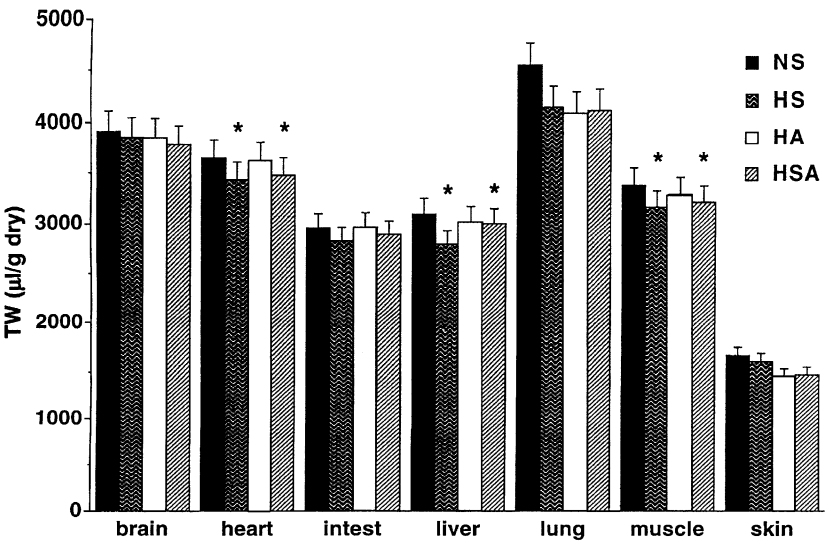

Fig. 6. Total tissue water (TW, means ± SE) for selected organs from anesthetized rats after 1 h of shock and 1 h of fluid resuscitation. Abbreviations are as in Fig. 1; intest, intestine. *$P < 0.05$, hypertonic saline effect.

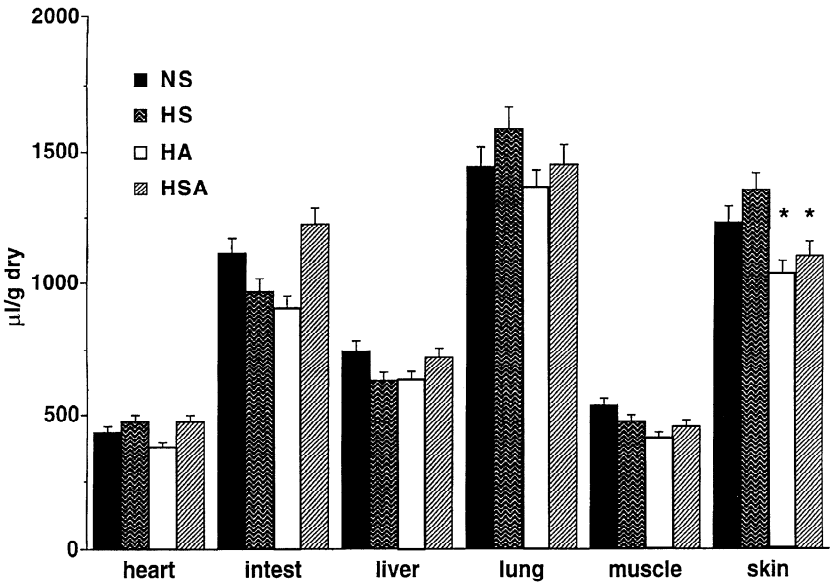

Fig. 7. Interstitial fluid volume (means ± SE) for selected organs from anesthetized rats after 1 h of shock and 1 h of fluid resuscitation. Abbreviations are as in Fig. 1. *$P \leq 0.05$, hyperoncotic albumin effect.

vascular resistance by a direct vasodilating effect of hypertonicity (5). Additionally, HS infusions may decrease venous capacitance (12), but this conclusion has been recently challenged (19). These mechanisms would lead to an increase in venous return and cardiac output and may account for the observed rapid increase in blood pressure in both HS and HSA groups. The apparent greater resuscitation effect with the combination of HSA is similar to other studies reporting that a combination of colloid and hypertonic crystalloid is more efficacious than either solution alone for restoration and maintenance of hemodynamics (9, 23, 25). It is possible that the differences in arterial blood pressure between NS and the other groups would also affect capillary perfusion pressures, especially if autoregulation was impaired. Therefore, a lower capillary pressure in the NS group might be needed to balance against a lowered colloid osmotic pressure and still maintain the same PV. In fact, total protein concentration did tend to be lower in the NS group compared with the other groups.

The type of fluid resuscitation clearly affects fluid compartments in different ways. There was a clear difference in the directional movement of fluid in animals receiving hypertonic saline solutions vs. animals receiving isotonic solutions. In seven of nine tissues, there was less total fluid accumulation and a smaller cell volume after HS administration (HS and HSA) compared with the other groups. Although all four solutions caused equal PV expansion, they achieved this by different mechanisms. The PV expansion with hypertonic solutions appears to be due to osmotic translocation of cell water out of cellular spaces. Although it has been discussed in many reviews and research papers, this is the first study we know of that directly measured mobilization of cellular water with hypertonic resuscitation after shock. These data agree with mathematical modeling based on data of plasma expansion, which assumed that HS pulls fluid equally out of all cells (14). This mathematical model also predicted a minimal reduction in the ISFV after HS (14). Results of the present study are consistent with

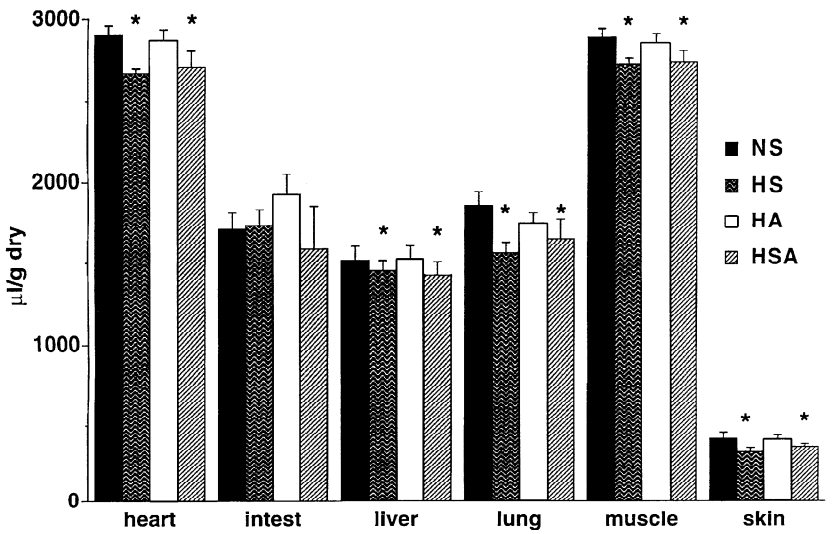

Fig. 8. Cell water (means ± SE) for selected organs of anesthetized rats after 1 h of shock and 1 h of fluid resuscitation. Abbreviations are as in Fig. 1. *$P \leq 0.05$, hypertonic saline effect.

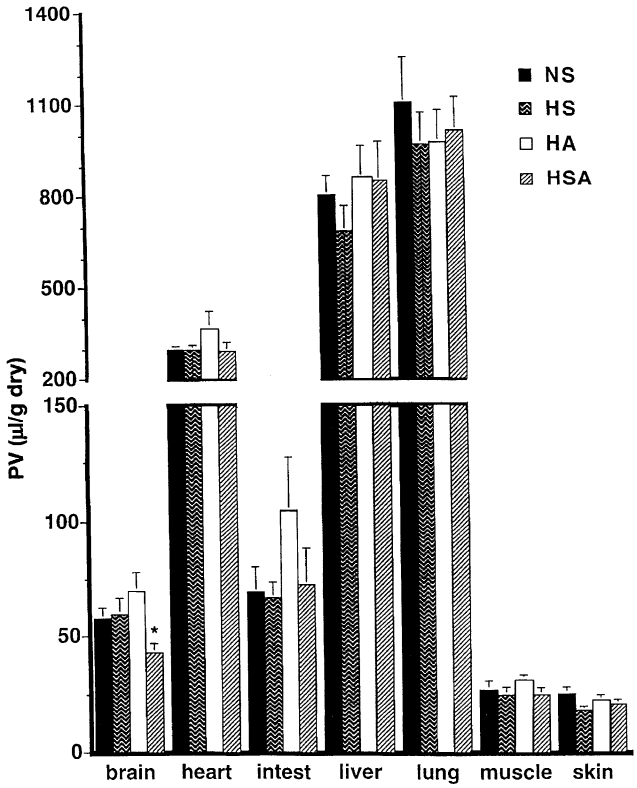

Fig. 9. Plasma volume (PV, means ± SE) for selected organs of anesthetized rats after 1 h of shock and 1 h of fluid resuscitation. Abbreviations are as in Fig. 1. *$P \leq 0.05$, significantly different between HSA and HA.

this model. Furthermore, direct visual measurements of endothelial cell size after shock and after HS infusion have also shown cell swelling during shock and shrinkage with HS (15).

Heart, muscle, lung, and skin showed statistically significant decreases in cell volume with HS. The functional effect of these changes in vital organs, such as the heart and lungs, was not evaluated, but the implications are intriguing. Myocardial edema may be occurring after hemorrhagic shock and conventional isotonic resuscitation (16). The smaller TW and cell volume in groups with HS suggests that this edema can be prevented or normalized. Decreased cell water might increase intracellular calcium concentration and be the mechanism of the observed positive inotropic effects (7). On the other hand, too rapid an electrolyte change from too quick a decrease in myocardial cell water may be one mechanism for the arrhythmias occasionally reported with HS administration (17).

An earlier study has shown the fluid composition of various tissues of normal rats prior to shock (16). The relative size of the different volume compartments was unique within specific tissue types (16). Specifically, it is clear that muscle, which has 80% of its water in its cellular space, is the primary organ from which fluid is drawn during hypertonic saline resuscitation. Skin, on the other hand, is composed primarily of interstitial tissue, and skin did respond differently than the other tissues to fluid therapy. Clinical impression has suggested that pitting edema occurs in patients resuscitated with large volumes of crystalloids, but peripheral edema is less with colloid administration. The concern of crystalloids causing interstitial edema is one factor that has led to the continued crystalloid vs. colloid controversy for the optimal fluid resuscitation regimen in critically ill patients. Therefore, it was interesting to note that the only tissue that showed a smaller ISFV with colloid resuscitation was the skin, with its large compositional interstitial space. Thus, although this tissue is visually very apparent and easily examined clinically, it appears that other tissues are either more resistant than the skin to expansion of their interstitial spaces after crystalloid resuscitation or less responsive to colloid therapy. The ISFV of the lung was not significantly different between resuscitation groups, although there was a trend for there to be less TW when colloids were administered. Thus evidence of pulmonary edema, as seen by increased lung water or increased interstitial volume, was not apparent and suggests that clinical pulmonary edema after fluid resuscitation may be due to a number of other factors rather than simply type of fluid resuscitation.

Tissue PV was not different among groups, except for brain, and interpretation of the brain results is not immediately evident. Results may be due to an unidentified organ-specific difference or due to the limitations of the tracer methods. It is possible that the blood-brain barrier affects ^{125}I distribution after shock. Because our pilot study did not evaluate steady-state levels in the brain, more work is required to evaluate the tracer techniques ability to measure fluid shifts within this tissue.

A critique of the present study is that not all groups reached target blood pressure equally well. One might predict that an even larger volume of NS would have been necessary; for example, to equal the blood pressure reached with the HSA. This additional volume of fluid would have enhanced the differences in the tissue fluid compartments.

The use of nephrectomized animals in this study is at variance with clinical resuscitation. Thus an important physiological response, diuresis, was unavailable for preventing overhydration and edema. Renal clearance of excess fluid may have decreased the amount of TW reported in the tissues of the NS group. However, HS actually causes a greater diuresis than NS or colloids (8, 23). Therefore, a large diuresis in the groups receiving HS and HSA would have only exaggerated the smaller TW and cell water seen in these groups, because even more fluid would have been removed. Rats with functional kidneys were not used in this study due to the technical difficulties that would have been encountered in maintaining a steady-state ^{51}Cr level and because of the imprecision involved in determining the exact ^{51}Cr dose in the animal due to rapid renal clearance of this compound. Thus, although the precise values of our data may be slightly biased by using anephric animals, the physiological effect of losing renal function for 3 h would not have had as great an impact on our study as the technical difficulties of using intact animals.

Despite these limitations, this study suggests possible beneficial effects of hypertonic saline solutions in situations of preexisting cellular edema. The determination of the ultimate clinical implications of the use of different resuscitation regimens, however, requires evaluation of organ function, acid-base status, and long-term morbidity and survivability.

In summary, all solutions restored PV, ECFV, and ISFV equally in the intact animal but did so through different mechanisms. Resuscitation with NS to a clinical endpoint, MAP, was slower and required significantly more fluid than any other group. The hypertonic saline solutions supported or produced normalization of cellular volume in lung, skin, and muscle. During the acute postresuscitation phase, there appears to be some protection against interstitial and cellular edema in vital organs during fluid resuscitation with hypertonic saline solutions. The long-term functional consequences of the fluid shifts for these solutions have not yet been defined.

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Address for reprint requests: P. F. Moon, Dept. of Clinical Sciences, College of Veterinary Medicine, Cornell Univ., Ithaca, New York 14853.

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