Hypertonic Saline Solution-Hetastarch for Fluid Resuscitation in Experimental Septic Shock

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Hypertonic colloid solutions have been found efficacious in the resuscitation from hemorrhagic/traumatic shock. The present study investigated the hemodynamic, gasometric, and metabolic effects of hypertonic colloids in endotoxic shock in the dog. Thirty minutes after administration of 3 mg/kg normal body weight of Escherichia coli *endotoxin, dogs were randomly assigned to receive 10 mL/kg hydroxyethylstarch (HES) either in 0.9% NaCl (HES, 10 dogs) or in 7.5% NaCl (HT-HES, 10 dogs) in 30 min. Thereafter, 0.9% NaCl solution was administered in volumes adequate to maintain pulmonary artery balloon-occluded pressure at baseline levels. Total fluid administered averaged 64 ± 30 mL/kg (mean ± SD) in the HES group and 73 ± 34 mL/kg in the HT-HES group. As these differences were not statistically significant, total sodium load was higher in the HT-HES group. The persistent volume effect was associated with persistently lower hematocrit and protein levels in the HT-HES group. Initial fluid resuscitation with HT-HES resulted in arterial pressure, cardiac filling pressures, cardiac output, stroke volume, and rates of oxygen delivery and oxygen consumption that were greater than those with HES. Vascular resistances were similar. Analysis of left ventricular function curves also indicated an improvement in cardiac performance. However, these effects almost completely vanished during the remainder of the study. In the HT-HES group, serum sodium and osmolality levels increased to 167 ± 4 mEq/L and 344 ± 4 mOsm/kg H_2O, respectively. Therefore, in the initial fluid resuscitation from septic shock, hypertonic colloids can have beneficial effects that are attributed to an increase in plasma volume and an improvement in cardiac function; but these effects are only transient.*

Key Words: SHOCK, SEPTIC—resuscitation. FLUID BALANCE.

Hypertonic saline solutions have been effectively used for many years in the fluid resuscitation of animals (experimentally) and of patients with severe hypovolemia (1–6). Possible mechanisms responsible for the beneficial effects seen with these solutions include increased plasma volume (7,8), improved myocardial contractility (9,10), widespread vasodilation (11,12), and an as yet ill-defined reflex mechanism causing a sustained hemodynamic improvement independent of significant volume expansion (13,14). In circulatory shock, these effects also could be related to the reversal of cellular abnormalities (15).

The role of hypertonic solutions in the treatment of septic shock is less well defined. Hypertonic solutions of glucose, insulin, and potassium (GIK) increase cardiac output and oxygen consumption in septic shock both experimentally (16,17) and clinically (18). However, these effects appear to be related to the hyperosmolarity rather than to the metabolic effects of the mixture (17). In a recent study from our laboratory (19), hypertonic saline solution was used in the treatment of experimental endotoxic shock and was found to restore oxygen transport and consumption rapidly (19). Another recent study of experimental endotoxic shock related the hemodynamic improvement to the total sodium load administered, whether it was given isotonically or hypertonically (20).

The combination of hypertonic saline solution with

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colloids has been suggested as enhancing the vascular effects of these fluids (6,21–23). In bled sheep, the combination of hypertonic saline solution with dextran has been found superior to a number of other solutions of equal tonicity in maintaining plasma volume, mean arterial pressure, and cardiac output (22). Kramer et al. (22) used hypertonic saline solution-dextran for small volume resuscitation of sheep with severe hemorrhagic shock and found cardiac output, oxygen consumption, and urine output to be significantly greater than those with resuscitation with the same volume of lactated Ringer's solution. These authors recently used the same solution in the resuscitation of severely injured patients and observed a more rapid hemodynamic stabilization associated with an improved survival (6).

To our knowledge, hypertonic colloid solutions have not been used in the resuscitation from septic shock. In the present study, we evaluated the hemodynamic, gasometric, and metabolic effects of 6% hydroxyethylstarch (HES) in 0.9% NaCl or in 7.5% NaCl used in the initial fluid resuscitation from septic shock. We used an endotoxin dog model in which fluid administration produces a low resistance type of shock (19,24,25).

Methods and Material

Twenty mongrel dogs (28 ± 7 kg) were randomly divided into two groups of 10 each, one group to receive HES in 0.9% NaCl (Plasmasteril, Fresenius AG) and one group to receive HES in 7.5% NaCl (after sterile addition of NaCl in the hospital pharmacy) for initial resuscitative fluid. After an overnight fast with water available, the dogs were anesthetized with intravenous pentobarbital 25 mg/kg. Anesthesia was maintained with additional intravenous doses of 15–30 mg as needed. Cuffed endotracheal tubes were inserted and the lungs ventilated with a volume-cycled ventilator (Siemens-Elema 900 Servo) at a rate of 12 breaths/min and an $F_{I_{O_2}}$ of 0.21. Tidal volume was adjusted to maintain P_{aCO_2} between 35 and 45 mm Hg. End-tidal CO_2 was monitored continuously (Capnograph 47210 A, Hewlett-Packard). Arterial and venous catheters (16G8, Becton, Dickinson and Co.) were placed surgically in the right femoral vessels and advanced to the distal aorta and inferior vena cava, respectively. A balloon-tipped flotation catheter (Swan-Ganz catheter model 93A-131H-7F, American Edwards Laboratories) was placed surgically in the right external jugular vein and advanced to the pulmonary artery. Position was confirmed by intravascular pressure waveforms. Heart rate and intravascular pressures were recorded (7404A recorder, Hewlett-Packard) on standard paper tracings. Cardiac output was measured by thermodilution technique with use of 5 mL of cold (<2°C) 5% dextrose in water at end-expiration. Three to six measurements were averaged. Blood gas tensions were measured by an automated analyzer (ABL2, Radiometer). Arterial and venous hemoglobin saturations were calculated and corrected for temperature and pH with use of Rossing and Cain's nomogram (26). The following baseline data were obtained before endotoxin administration: arterial pressure (AP), pulmonary artery pressure (PAP), pulmonary artery balloon-occluded pressure (PAOP), and right atrial pressure (RAP), cardiac output (CO), arterial and mixed venous blood gas tensions, hemoglobin and hematocrit, plasma protein and serum electrolyte levels, serum osmolarity, and arterial lactate concentration. After this, *E. coli* endotoxin (lipopolysaccharide *W. E. coli* 055:B5, Difco) 3 mg/kg was slowly injected (over 1 min) IV. Zero time (T_0) was taken as the start of this injection. The dogs were undisturbed for 30 min, after which all baseline measurements were repeated (T_{30}). The dogs were then given the appropriate initial resuscitative fluid according to prior randomization at 20 $mL \cdot kg^{-1} \cdot hr^{-1}$ for 30 min. At the end of this infusion (T_{60}), all baseline measurements were again repeated. Resuscitation was continued in both groups with 0.9% NaCl with the rate of infusion adjusted every 10 min to maintain PAOP at baseline (preendotoxin) levels. Intravascular pressures, cardiac output, arterial and mixed venous blood gas tensions were measured every hour. All baseline measurements were repeated at 240 min before the 0.9% NaCl infusion and mechanical ventilation were discontinued. Intravenous catheters were removed, wounds closed, and the dogs returned to their cages with tracheal tube still in place. The dogs were observed the morning after to determine mortality.

Stroke volume (SV), systemic (SVR) and pulmonary (PVR) vascular resistance, left (LVSW) and right (RVSW) ventricular stroke work, oxygen delivery (O_2del) and consumption ($\dot{V}O_2$), alveolar-arterial oxygen gradient ($A\text{-}aO_2$), and venous admixture ($\dot{Q}s/\dot{Q}t$) were calculated by the following formulas:

$$SV\ (mL) = CO/HR,$$

$$SVR\ (dynes \cdot sec \cdot cm^{-5}) = (AP - RAP) \times 80/CO,$$

$$PVR\ (dynes \cdot sec \cdot cm^{-5}) = (PAP - PAOP) \times 80/CO,$$

$$LVSW\ (g/m) = SV \times (MAP - PAOP) \times 0.0136,$$

Table 1. Fluid and Sodium Intake in the Two Groups of Dogs

	Time intervals (min)			
	T_{30}–T_{60}	T_{60}–T_{120}	T_{120}–T_{180}	T_{180}–T_{240}
Fluid intake (mL/kg)				
HES	10.0	24 ± 12	20 ± 12	10 ± 10
HT-HES	10.0	21 ± 12	22 ± 12	20 ± 17
Sodium intake (mEq/kg)				
HES	1.5	3.8 ± 1.9	3.2 ± 2.1	1.7 ± 1.8
HT-HES	12.0	3.3 ± 1.9	3.4 ± 2.0	3.1 ± 2.8

$$RVSW\ (g/m) = SV \times (PAP - RAP) \times 0.0136,$$

$$O_2del\ (mL/min) = (CO \times CaO_2) \times 10,$$

$$\dot{V}O_2\ (mL/min) = CO \times (CaO_2 - C\bar{v}O_2) \times 10,$$

$$A\text{-}aO_2\ (mm\ Hg) = (PBar - 47) \times 0.21 - PO_2 + PCO_2/0.8,$$

$$\dot{Q}s/\dot{Q}t\ (\%) = (CcO_2 - CaO_2)/(CcO_2 - C\bar{v}O_2),$$

where CcO_2, CaO_2, and $C\bar{v}O_2$ represent the oxygen contents of pulmonary capillary and arterial and mixed venous blood, respectively. Cardiac output, SV, LVSW, RVSW, O_2del, and $\dot{V}O_2$ were referred to the weight of each dog.

Statistical evaluation was performed by a multivariate analysis of variance (MANOVA, SPSS update 9.0) for repeated measures designs, to evaluate the effects of time and treatment. Differences in fluids infused were evaluated by a Student's *t*-test for unpaired data. Differences in survival were evaluated by a χ^2 analysis. A 95% confidence level was accepted for statistical signification. Results are expressed as mean ± SD.

Results

Total fluid administered was 64 ± 30 mL/kg in HES and 73 ± 34 mL/kg in HT-HES (differences not significant). As there were no significant differences in sodium administered after initial resuscitation, total sodium load was higher in HT-HES (Table 1).

As anticipated, endotoxin administration was immediately followed by significant decreases in arterial pressure, filling pressures, and cardiac output (Figures 1 and 2). With initial fluid resuscitation, cardiac filling pressures increased more after HT-HES than after HES. Thereafter, they returned to baseline levels as part of the protocol (Figure 1). In the HT-HES group, arterial pressure also increased transiently; although this increase did not reach statistical significance (Figure 1). Pulmonary artery pressure followed

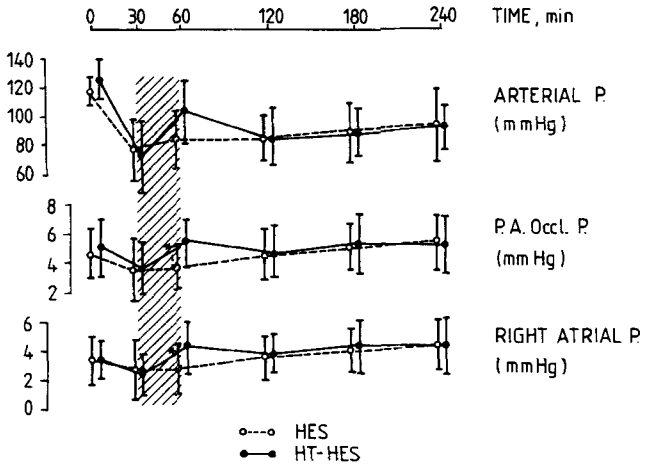

Figure 1. Changes in arterial pressure, pulmonary artery balloon-occluded pressure, and right atrial pressure over time in the dogs initially resuscitated (period represented by the shaded area) with normotonic HES (open circles, broken lines) or hypertonic HES (closed circles, continuous lines). Thereafter, all dogs were treated with normotonic saline solution. *$P < 0.05$ between the two groups of animals.

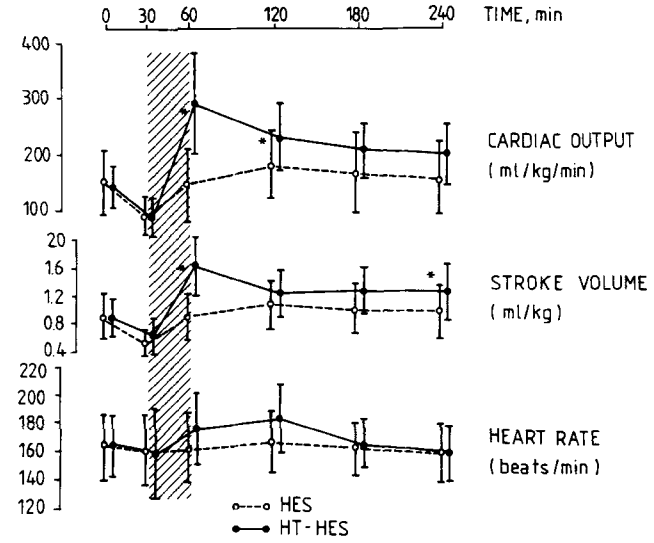

Figure 2. Evolution of cardiac output, stroke volume, and heart rate in the two groups of animals (see Figure 1).

a similar pattern. In the HT-HES group, heart rate was slightly higher after initial fluid resuscitation (Figure 2). Cardiac output was higher in the HT-HES group with the differences being significant at 60 and 120 min (Figure 2); it was also significantly above baseline at these times. Stroke volume followed a comparable course with differences being significantly greater also at the end of the study (Figure 2). During fluid infusion, systemic vascular resistance decreased significantly in both groups and remained decreased (Figure 3). There were no significant differences in systemic or pulmonary vascular resistance between the two groups.

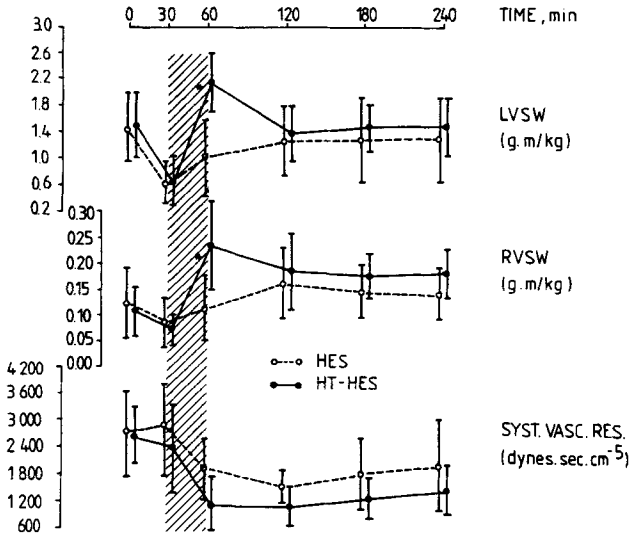

Figure 3. Changes in left ventricular stroke work, right ventricular stroke work, and systemic vascular resistance over time in the two groups of animals (see Figure 1).

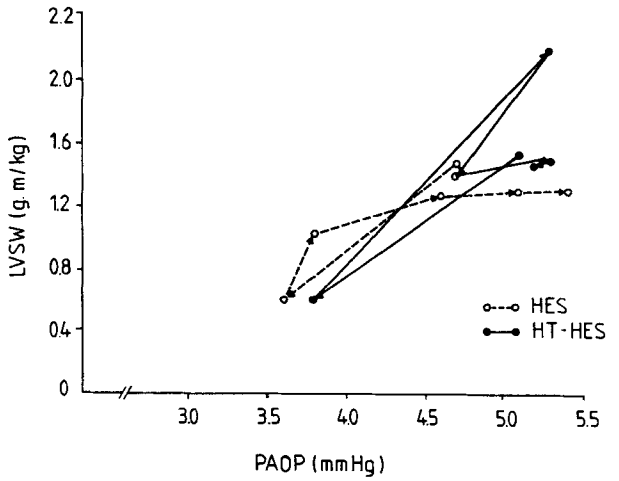

Figure 4. Left ventricular function curves represented by left ventricular stroke work versus pulmonary artery balloon-occluded pressure in the dogs treated with normotonic HES (open circles, broken lines) and with hypertonic HES (closed circles, continuous lines). The time intervals are the same as those in preceding figures. During initial fluid resuscitation (from the second to the third points), left ventricular function increased significantly more in the hypertonic group.

At the end of the initial fluid resuscitation, both left ventricular and right ventricular stroke works were substantially higher after HT-HES (Figure 3). This suggested that cardiac performance improved, as pulmonary-artery balloon-occluded pressure, reflecting left ventricular end-diastolic pressure, reached values similar to those observed later during the study. This improvement in cardiac function, however, appeared transient (Figure 4).

After initial fluid resuscitation, the rate of oxygen delivery was higher in the HT-HES group and was associated with a greater oxygen consumption (Figure 5). Each dog had significant increases in blood lactate levels after endotoxin followed by some decrease with fluid resuscitation, but there were no significant differences between the two groups of animals (Table 2). Both groups had significant and similar increase in A-aO_2 and Qs/Qt during the study (Table 2 and Figure 5).

Hematocrit increased significantly in all dogs after endotoxin administration; it remained elevated in the HES group and decreased significantly in the HT-HES group (Table 2). Total serum protein levels decreased in both groups during the study but the decrease was greater in the HT-HES group. After HT-HES, serum sodium levels increased to 167 ± 4 mEq/L (range 159–172 mEq/L) and serum osmolarity to 344 ± 4 mOsm/kg H_2O (range 337–349 mOsm/kg H_2O). In the HES group, neither serum sodium nor osmolarity levels changed significantly. In the HT-HES group, serum potassium concentration decreased significantly but transiently to 2.8 ± 0.6 mEq/L (Table 2).

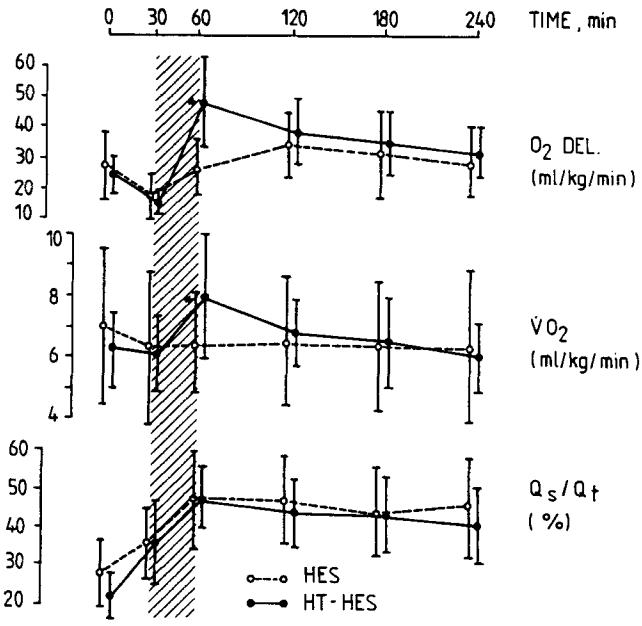

Figure 5. Evolution of O_2 delivery, O_2 consumption, and venous admixture in the two groups of animals (see Figure 1).

Three dogs in the HT-HES group and one dog in the HES group survived to the next morning. This difference in survival was not statistically significant.

Discussion

Hypertonic saline solutions can rapidly restore intravascular volume by pulling water from the intracel-

Table 2. Biochemical Changes Observed during the Study

	T_0	T_{30}	T_{60}	T_{240}
Hematocrit (%)				
HES	44 ± 7	51 ± 8[a]	52 ± 9[a]	48 ± 8[a]
HT-HES	40 ± 5	48 ± 8[a]	44 ± 7[b]	42 ± 10
Proteins (g/dL)				
HES	6.1 ± 0.7	5.9 ± 0.8[a]	4.6 ± 0.7[a]	3.9 ± 0.8[a]
HT-HES	5.8 ± 0.5	5.7 ± 0.7	3.9 ± 0.5[a,b]	3.5 ± 0.6[a]
Osmolarity (mOsm/kg H_2O)				
HES	307 ± 10	307 ± 9	309 ± 9	306 ± 7
HT-HES	297 ± 4	299 ± 5	344 ± 4[a,b]	326 ± 4[a,b]
Sodium (mEq/L)				
HES	150 ± 5	148 ± 5	147 ± 5	150 ± 5
HT-HES	145 ± 3	145 ± 2	167 ± 4[a,b]	161 ± 2[a,b]
Potassium (mEq/L)				
HES	3.5 ± 0.5	3.6 ± 0.5	3.3 ± 0.5	4.0 ± 0.6
HT-HES	3.5 ± 0.6	3.3 ± 0.6	2.8 ± 0.6[b]	4.0 ± 1.0
Lactate (mEq/L)				
HES	1.3 ± 0.5	4.3 ± 1.6[a]	3.9 ± 1.6[a]	3.1 ± 1.5[a]
HT-HES	2.4 ± 1.6	4.7 ± 2.2[a]	4.4 ± 2.0[a]	3.1 ± 1.6
A-aDO_2 (mm Hg)				
HES	24 ± 9	33 ± 12[a]	27 ± 10	26 ± 13
HT-HES	20 ± 13	32 ± 13	17 ± 13	28 ± 12

[a] $P < 0.05$ from baseline (T_0); [b] $P < 0.05$ between HES and HT-HES.

lular space into the interstitial and intravascular spaces (7). Hypertonic saline solutions may also improve myocardial performance by a direct effect on contractility (8–10) or by widespread precapillary vasodilation (11,12). Some hemodynamic effects can also result from a vagally mediated reflex mechanism triggered by the passage of hypertonic fluid through the pulmonary vascular bed (13,14). During shock states, improved myocardial performance can also be due to decreases in myocardial cell edema and restoration of myocardial cell transmembrane potentials (15,17).

In hemorrhagic shock, the combination of hypertonic saline solution with colloids provides both experimentally (22,23) and clinically (6) a greater and more sustained hemodynamic improvement than normotonic solutions. The proposed explanation is that the addition of colloids increases the plasma volume expansion. As fluid repletion remains a cornerstone in the management of septic shock and as colloids are often used in the early resuscitation of shock states, we compared the use of a given amount of colloids prepared either in normotonic or in hypertonic saline solution. We selected 6% hetastarch as the colloid component because it is both effective and safe even with relatively large volumes (27–29) and offers substantial cost advantages over albumin. We used 7.5% NaCl as the hypertonic saline solution component because this concentration appears to induce the maximal hemodynamic effects with overt toxicity (30). For this initial fluid resuscitation, we infused a standard amount of 10 mL/kg of colloid fluids, as this corresponds to the initial fluid requirements in this dog model (19,24,25).

The total amount of fluids required was not reduced in the dogs initially given HT-HES. This is surprising in view of the expected volume effect of the saline solution load, which was also associated with a significant increase in cardiac filling pressures. This also contrasts with previous studies in animals (20) and in humans (2–4,21) in which hypertonic solutions significantly decreased fluid requirements for resuscitation. This difference could be explained by an only transient volume effect of hypertonic solution in our model where fluid requirements were very high. However, the volume effect of HT-HES appeared maintained in view of the persistently lower proteins and hematocrit levels in this group. Hence, a larger blood volume was maintained in the presence of similar intravascular pressures, suggesting greater cardiovascular compliance, possibly related to a reduction of cellular edema with hyperosmolar solutions (7,17). It is also consistent with the vasodilating effect of those hypertonic solutions (11,12), although the lack of differences in vascular resistances plays down this phenomenon.

Cardiac output increased markedly after HT-HES to levels higher than those of baseline. The higher sodium load and the concurrent increase in cardiac filling pressures indicate that this was primarily due to a volume effect. The study of the left and the right ventricular function, however, also revealed a positive effect of the hypertonic solution on cardiac per-

formance. An improvement in myocardial contractility could be related to a direct hyperosmolar effect (9,10), to a restoration of altered myocardial transmembrane potentials (15), or a decrease in myocardial edema (17). This latter mechanism, however, was unlikely as it occurred early and was only transient.

The higher cardiac output associated with hypertonic HES was accompanied by increases in oxygen transport and oxygen consumption, presumably reflecting a concurrent improvement in tissue blood flow (31,32). Thus, hypertonic solutions could shorten the cellular ischemia or hypoxia. Although plasma lactate levels tended to be lower in HT-HES, they were not significantly different in the two groups. Survival was also not significantly different between the two groups. Hence, the transient increase in oxygen delivery above baseline levels and the persistent volume effect of the hypertonic fluid were not shown to be beneficial.

Administration of hypertonic HES significantly increased serum sodium and osmolarity, which remained within relatively narrow ranges that would be clinically acceptable. Similar levels of serum sodium and osmolarity have been previously reported in human studies using hypertonic saline solution without adverse effects (3,4,33). Hypokalemia also occurred transiently and was probably due to an intracellular potassium shift, as it resolved spontaneously.

Hypertonic solutions can also have potentially beneficial effects in the presence of cerebral edema (34,35). They can also improve the distribution of pulmonary blood flow in the presence of acute lung injury (36,37). In the present study, hypertonic HES had no significant effect on blood gas tensions. Despite considerable venous admixture in this model, the formation of pulmonary edema is limited after endotoxin administration in the dog (38).

Our data indicate that hypertonic colloid solutions increase arterial pressure and cardiac output in the early resuscitation from septic shock. These effects appear related both to a volume effect and to an improvement in cardiac function. Hypertonic saline colloid solutions, therefore, offer a possible means for rapid restoration of hemodynamic stability in septic shock. However, the hemodynamic changes are largely transient, even though the effects on blood volume appear to persist. The long-term beneficial effects in the course of septic shock remain to be demonstrated.

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