Circulatory Shock 29:193–204 (1989)

Resuscitation of Conscious Pigs Following Hemorrhage: Comparative Efficacy of Small-Volume Resuscitation

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Efficacy of small-volume resuscitation (4 ml/kg) with 7.5% NaCl in 6% Dextran 70 (HSD), 7.5% NaCl (HS), dextran (D), and 0.9% NaCl (NS) was evaluated in conscious swine bled 37.5 ml/kg over 60 min. Hemorrhage reduced cardiac index (CI), stroke volume (SV), and mean arterial pressure (MAP). Four-hour survival after HSD (67%) was significantly ($P < 0.05$) greater than after HS (25%), D (17%), or NS (0%). The superior performance of HSD, and to a lesser extent HS, was associated with rapid plasma volume expansion, improved CI and SV, and decreased heart rate. The acute increases in cardiac index and stroke volume were greater following treatment with HSD and the improvement persisted for 4 hr. HSD also produced a transient increase in MAP. Plasma Na+ concentration and osmolality were increased to a similar extent with HSD and HS, while plasma K+ levels were initially decreased, returning to control levels within 60 min. HSD appears to be a superior small-volume resuscitation solution compared to the other treatments with no detrimental effects.

Key words: plasma electrolytes, osmolality, blood pressure, lethal hemorrhage, cardiac output, stroke volume, heart rate, conscious swine

Submitted for publication May 6, 1988; revised May 17, 1989.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official nor do they reflect the views of the Department of the Army or the Department of Defense (AR 360-5).

The studies described in this report were reviewed and approved by the Institutional Review Committee/ Animal Care and Use Committee at Letterman Army Institute of Research. The manuscript was peer-reviewed for compliance prior to submission for publication.

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INTRODUCTION

Hemorrhage is one of the major causes of death following trauma [1,2]; thus, rapid restitution of blood volume and therefore cardiovascular function are of paramount importance. Infusing small volumes (4 ml/kg) of hypertonic and/or hyperoncotic solutions is effective in improving cardiovascular function following hemorrhage in a variety of species including humans [3–20]. Hypertonic solutions alone cause initial, transitory improvements [7–12], and these effects can be sustained by the addition of hyperoncotic colloids [11–14]. The effectiveness of hypertonic/hyperoncotic solutions has been attributed to a mobilization of fluids from the extra- to the intravascular space [7,8,11,13]. While many studies have demonstrated the efficacy of these solutions in correcting the decrements in cardiovascular function following hemorrhage [5,6,12,16], few studies have addressed their efficacy in improving survival. In this study of conscious swine subjected to a normally lethal, fixed-volume blood loss, we investigated the functional consequences of post-hemmorrhage resuscitation with small volumes of isotonic saline (NS), hypertonic saline (HS), hyperoncotic colloid (D), or a combination hypertonic/oncotic solution (HSD). Cardiovascular adjustments, and fluid and electrolyte shifts were measured to assess their possible roles in promoting survival.

MATERIALS AND METHODS

Twenty-eight immature Yorkshire pigs were used in this study. They were obtained from a commercial breeder, and they were housed in a common indoor laboratory holding facility for 1 to 3 weeks prior to experimentation. Purina Pig Chow (Ralston Purina Co., St. Louis, MO) and water were provided ad libitum.

Seven to ten days before the study, after an overnight fast, each pig was transported to the operating room and administered a preanesthetic intramuscular injection of atropine sulfate (0.8 mg/kg), ketamine HCl (2.2 mg/kg), and 2.2 mg/kg xylazine (2.2 mg/kg). Halothane anesthesia was introduced by snout mask and maintained with an endotracheal catheter. A celiotomy was performed, the spleen was removed [21], and a polyvinylidine sideport catheter [22] was implanted in the abdominal aorta for blood removal during hemorrhage. The free end of this catheter was tunneled under the skin and exited at the midlumbar region of the back. Catheters were implanted in the carotid and pulmonary arteries through a neck incision. Catheter placement was confirmed by noting the desired pressure wave form. The free ends of these catheters were tunneled under the skin and exited on the dorsal surface of the neck. Catheters were used for hemodynamic measurements and blood sampling, and were filled with heparinized saline (100 U/ml). The exit sites were protected with Velcro patches sutured to the skin. The animal was observed throughout post-operative recovery and then returned to its holding cage. In addition, each pig was trained for 1 hr daily to accept physical restraint in a modified Pavlov sling and a respiratory snout mask. The training commenced 3 days before surgery and was reinstituted 2 days thereafter.

On the day of the experiment, following an overnight fast, each pig was transported to the laboratory, placed in the sling, and fitted with the snout respiratory mask, which was connected with a one-way Rudolph valve and 2.5 cm tubing to a

Horizon System metabolic cart for measurements of oxygen consumption. The carotid artery catheter was connected to a Statham P23Db transducer and pressure was recorded with a Gould model 2400 recorder. After a period of 30–60 min, in which the animal rested quietly in the sling and exhibited stable values of oxygen consumption, the experiment was begun. Three sets of control measurements were taken at 10 min intervals. Following the last control measurement, a continuous fixed-volume hemorrhage was started from the abdominal aorta catheter. The hemorrhage schedule was designed to simulate a blood loss as might occur in a severed artery in an extremity, the loss stopped mechanically after 1 hr. Accordingly, successive 7.5 ml/kg increments were drawn continuously, with increments being completed after 9, 19, 31.5, 44, and 60 min. Total blood loss was 37.5 ml/kg. Measurements were repeated at the end of each increment of blood loss. Immediately after hemorrhage, the animal was randomly assigned to one of the following treatment groups:

1. Normal saline (NS): 0.9% NaCl ($n = 8$, 24.5 ± 1.6 kg).
2. Dextran (D): 6% Dextran 70 in 0.9% NaCl ($n = 6$, 21.7 ± 1.0 kg; Macrodex, Pharmacia Laboratories, Piscataway, NJ).
3. Hypertonic saline (HS): 7.5% NaCl ($n = 8$, 24.3 ± 1.1 kg).
4. Hypertonic saline/dextran (HSD): 7.5% NaCl in 6% Dextran 70 ($n = 6$, 25.2 ± 1.7 kg).

The treatment solution was injected as a bolus (4 ml/kg over 1 min) into the pulmonary artery. All measurements were then repeated at 5, 15, 30, 60, 120, 180, and 240 min after injection. At each time point, blood samples (30 ml arterial and 3 ml venous) were taken and partitioned into chilled test tubes and placed in ice water for later determinations. Samples obtained during the control and hemorrhage periods were included in the hemorrhage volume.

Hemoglobin and oxygen content were measured with an Instrumentation Laboratory cooximeter, Model 282. Plasma sodium and potassium concentrations were determined with an Instrumentation Laboratory flame photometer. Plasma osmolality was determined with an Advanced Instruments osmometer, Model 3DII, and oncotic pressure with a Wescor colloid osmometer, Model 4100. Plasma protein concentration was measured with an American Optical refractometer.

Cardiac index was calculated by the Fick equation. Heart rate was determined from the pulse pressure tracing. Stroke index, total peripheral resistance, and left ventricular work were calculated from standard equations. Alterations in plasma volume were calculated from changes in hematocrit and hemoglobin concentration.

All parametric data obtained during hemorrhage and the first 5 min of resuscitation were evaluated with two-factor analyses of variance adjusted for repeated measures. The time effects for the HSD group over the first hour of resuscitation were assessed using single-factor analyses of variance for repeated measures. Significant differences between mean values were determined by Newman-Keuls tests. The survival data were analyzed using Breslow statistics for testing the equality of survival curves. Changes were considered significant when $P < 0.05$. Values presented in the text are means $\pm$ SEM.

RESULTS

Survival

Compared with the other resuscitation solutions, the combination of hypertonic saline/dextran (HSD) significantly ($P < 0.05$) improved survival of pigs subjected to lethal levels of blood loss (Fig. 1). In contrast, only 5 of 8 animals in the NS group were alive at 10 min into the recovery period, and all had died by 40 min. Administration of dextran (D) did not significantly improve survival (1 of 6 survived). Hypertonic saline (HS) did have a significant effect on survival (2 of 8 survived) but only when the group was compared to NS treated animals.

Death was attributable to either a failure of resuscitation to effect beneficial functional changes of sufficient magnitude to sustain life (NS, D), or a failure to sustain beneficial effects that were initially elicited (HS, HSD). In all instances, impending death of an animal was signaled by a progressively more pronounced decrease in cardiac output and mean arterial pressure.

Animal deaths seriously compromised our ability to obtain a statistical comparison of the 4 groups during the recovery period. In fact, it was only at the 5 min point of the recovery period that all groups were still intact. Consequently, between-group comparisons were limited to values obtained before hemorrhage, end of hemorrhage, and at 5 min post-treatment. Since only 2 animals died in the HSD group, one at 70 min and the other at 190 min after treatment, group characteristics during the recovery period could be more extensively studied. In some instances mean values and between-animal variance for this group were affected by loss of an animal. To compensate for this distortion, two mean values were calculated for the time points immediately preceding death: one mean included and the other excluded the nonsurviving animal (Figs. 2, 3).

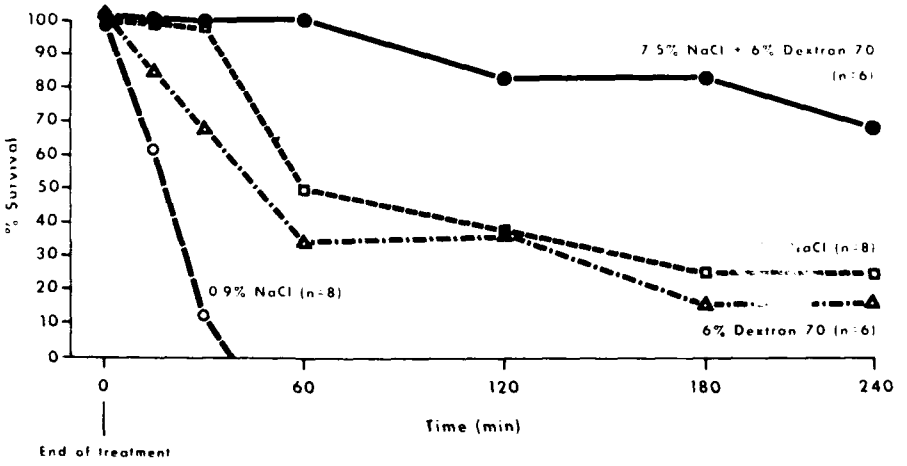

Fig. 1. Percent survival following small-volume (4 ml/kg) resuscitation for hemorrhagic hypotension with normal saline (n = 8), dextran (n = 6), hypertonic saline (7.5% NaCl; n = 8), and hypertonic saline/dextran (7.5% NaCl in 6% Dextran 70; n = 6). Hypertonic saline/dextran improved survival compared to all other groups, while hypertonic saline alone was greater than control.

RESPONSES TO HEMORRHAGE AND RESUSCITATION

There were no significant differences ($P > 0.05$) between groups in any of the measured variables prior to, or at the end of hemorrhage (Tables I, II). Cardiac index was reduced to a similar degree in all groups during hemorrhage (Table I).

Five minutes following treatment, cardiac index was increased in animals administered HSD and HS solutions. However, there was a significant between-group difference in the improvement; cardiac index increased 46 ± 6 ml/min/kg with HS and 104 ± 9 ml/min/kg with HSD. At 5 min after treatment with HSD, the cardiac index was equivalent to control values. Thereafter, cardiac index fell but was persistently greater than the level recorded at the end hemorrhage (Fig. 2).

Mean arterial pressure decreased in all groups during hemorrhage (Table I), and was immediately and significantly increased after administering HSD, but to levels that were significantly below those recorded during the control period. Thereafter, it fell to a level that was not different from that seen at the end of hemorrhage. Administration of NS, D, or HS had no significant effect on mean arterial blood pressure.

Heart rate was increased and stroke volume was decreased during hemorrhage (Table I). Although the magnitude of the increase in heart rate during hemorrhage was variable between groups, a significant difference was not noted. Heart rate was reduced 5 min after resuscitation with HS and HSD (Table I), but during the subsequent recovery period values for the HSD group reverted to levels similar to those recorded at the end of hemorrhage. The decrements in heart rate were accompanied by increments in stroke volume (Fig. 2), but the latter effect was significantly greater in the HSD group than in the HS group. The change in stroke volume following administration of HSD did not persist throughout the recovery period; it fell over the recovery period but was maintained at values greater than those seen at the end of hemorrhage.

Total peripheral resistance was unchanged during hemorrhage, but was promptly reduced following administering of HS or HSD (Table I). During the remainder of the recovery period following HSD, total peripheral resistance increased, returning to prehemorrhage control levels (Fig. 2). Left ventricular work was acutely elevated following the HSD administration, but fell over the remaining period of recovery (Fig. 2).

Plasma sodium concentrations were not altered during hemorrhage nor following treatment with NS or D (Table II); however, both hypertonic solutions significantly increased plasma sodium levels, 11 ± 1 mEq/L with HS and 8 ± 1 mEq/L with HSD. In the HSD group, these increases persisted through the recovery period (Fig. 3). Plasma potassium tended to rise during hemorrhage, but was not significantly altered. However, within 5 min after treatment with NS, a significant increase in plasma potassium was noted. Plasma potassium, while initially decreased after both HS and HSD administration, returned to control levels by 60 min (Fig. 3).

Plasma osmolality was increased during hemorrhage and was further increased by the HS and the HSD, an effect that persisted throughout the recovery period. In all four groups plasma oncotic pressure was progressively decreased during hemorrhage, the decrements ranging from 4.0 to 2.5 mmHg. Treatment with D returned plasma oncotic pressure to control levels, whereas HS produced a further reduction of

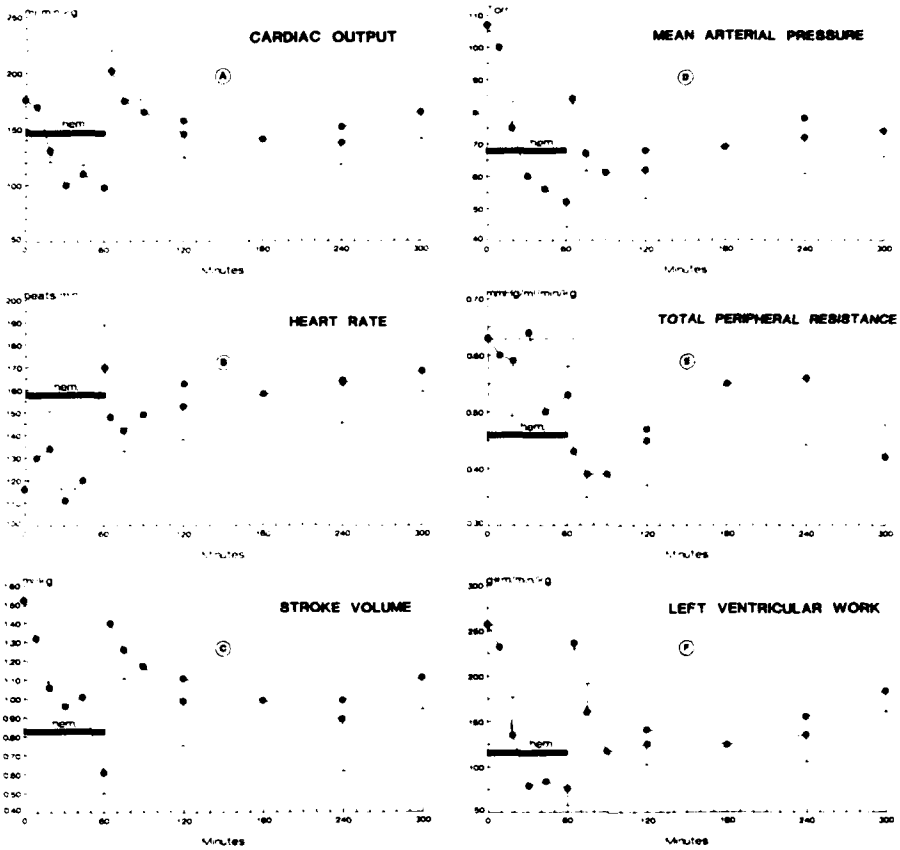

Fig. 2. Effects of progressive fixed-volume hemorrhage (37.5 ml/kg) followed by resuscitation with 7.5% NaCl in 6% Dextran 70 on cardiovascular function. Resuscitation was provided (over 1 min) after hemorrhage. Breaks in the plots indicate time points at which mean and SEM values were calculated to include as well as exclude animals that died shortly thereafter. The solid bar depicts hemorrhage interval and the dashed line control levels for each variable.

2.3 ± 0.6 mmHg. Five minutes following treatment with HSD, oncotic pressure was not changed. However, over the remainder of the recovery period it rose significantly compared to the levels recorded at the end of hemorrhage.

Plasma protein concentrations were decreased over the hemorrhage (Table II), and treatment with either hypertonic saline solution resulted in a further reduction (0.7 ± 0.2 g/dl with HS and 0.6 ± 0.1 g/dl with HSD). Over the recovery period following HSD administration, plasma protein levels were significantly increased (Fig. 3).

Hemorrhage progressively decreased hematocrit and hemoglobin levels, and immediately after all treatments except NS, further decrements were observed (Table

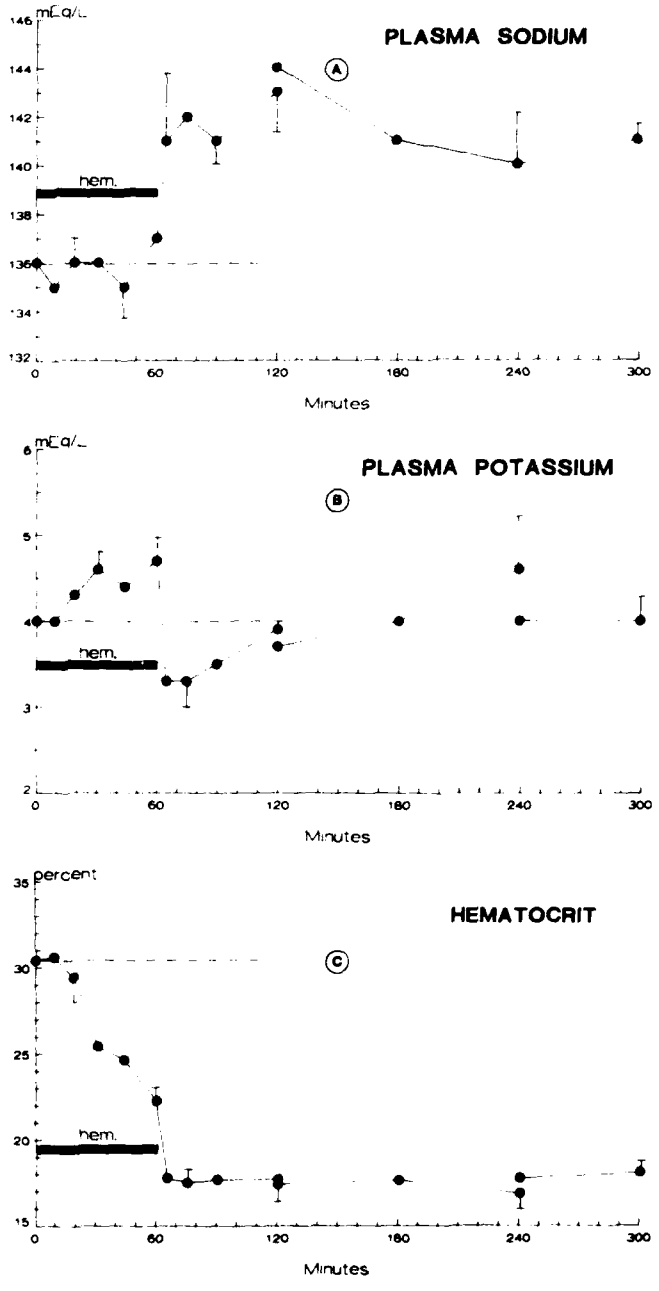

Fig. 3. Effects of progressive fixed volume hemorrhage followed by resuscitation with hypertonic saline/dextran on plasma sodium and potassium concentrations and hematocrit levels. See Figure 2 for details.

TABLE I. Hemodynamic Changes From Control (C), After Hemorrhage (H), and 5 Minutes After Small-Volume Resuscitation (T)

	NS[a]	D[b]	HS[c]	HSD[d]
Cardiac index (ml/kg/min)				
C	150 ± 8	132 ± 9	167 ± 8	177 ± 16
H	91 ± 13*	18 ± 13*	77 ± 12*	98 ± 14*
T	104 ± 13*	107 ± 20*	123 ± 7*,**	202 ± 19**
Mean arterial pressure (mmHg)				
C	105 ± 6	99 ± 4	103 ± 3	107 ± 3
H	55 ± 3*	62 ± 7*	54 ± 4*	52 ± 8*
T	56 ± 5*	62 ± 3*	65 ± 3*	84 ± 4*,**
Heart rate (beats/min)				
C	113 ± 3	110 ± 5	115 ± 4	116 ± 4
H	204 ± 20*	191 ± 15*	185 ± 15*	170 ± 19*
T	214 ± 17*	187 ± 15*	158 ± 12*,**	148 ± 13*,**
Stroke index (ml/kg/min)				
C	1.23 ± 0.05	1.22 ± 0.10	1.47 ± 0.13	1.52 ± 0.14
H	0.57 ± 0.08*	0.44 ± 0.07*	0.42 ± 0.06*	0.61 ± 0.10*
T	0.59 ± 0.07*	0.60 ± 0.13*	0.83 ± 0.09*,**	1.40 ± 0.16*,**
Total peripheral resistance				
C	0.72 ± 0.04	0.77 ± 0.08	0.62 ± 0.03	0.63 ± 0.07
H	0.64 ± 0.05	0.88 ± 0.17	0.76 ± 0.10	0.53 ± 0.05
T	0.61 ± 0.07	0.71 ± 0.14	0.53 ± 0.03**	0.43 ± 0.03**
Left ventricular work (dynes/cm^2)				
C	220 ± 31	176 ± 10	233 ± 13	257 ± 25
H	72 ± 12*	68 ± 14*	57 ± 11*	76 ± 22*
T	87 ± 17*	91 ± 18*	109 ± 9*	236 ± 32**

[a]NS = normal saline ("isotonic" in text).
[b]D = dextran.
[c]HS = hypertonic saline.
[d]HSD = hypertonic saline/dextran.
*Significantly different from C ($P < 0.05$).
**Significantly different from H ($P < 0.05$).

II). During the subsequent recovery period no additional changes in hematocrit (Fig. 3) or hemoglobin were observed in the HSD group (Fig. 3). The ratio of hemoglobin to hematocrit was not significantly altered by hemorrhage or HSD, being 0.304 ± .003 before hemorrhage, 0.296 ± 0.014 at the end of hemorrhage, and 0.298 ± 0.012 at 5 min after treatment. The calculated acute increases in plasma volume 5 min after treatment were 6.6% ± 2.7% with NS, 21.7% ± 2.5% after D, 29.5% ± 2.6% following HS, and 32.6% ± 2.4% with HSD. The increase in plasma volume following HSD persisted throughout the 4 hr of recovery.

DISCUSSION

The improvement of survival after resuscitation with HSD is consistent with earlier work reported by Maningas et al. [12]. These investigators, however, did not observe improved survival with HS alone, as others have [5,6,16], and did not show a significantly greater effect with the combination solution compared to D alone. In our study, HS also improved survival, but to a lesser extent than HSD. D alone failed

TABLE II. Blood and Plasma Constituents From Control (C), After Hemorrhage (H), and 5 Minutes After Treatment With Small Volume Resuscitation (T)

	NS[a]	D[b]	HS[c]	HSD[d]
Na^+ (mEq/L)				
C	136 ± 2	137 ± 2	140 ± 2	138 ± 2
H	139 ± 2	133 ± 3	138 ± 1	135 ± 2
T	139 ± 2	135 ± 3	149 ± 1*,**	143 ± 3*,**
K^+ (mEq/L)				
C	4.2 ± 0.1	4.1 ± 0.1	4.2 ± 0.2	4.0 ± 0.1
H	5.3 ± 0.2	4.8 ± 0.5	5.0 ± 0.3	4.7 ± 0.3
T	5.7 ± 0.4*	4.4 ± 0.8	3.6 ± 0.2**	3.3 ± 0.3*,**
Osmolality (mOsm/kg)				
C	277 ± 1	280 ± 1	281 ± 1	279 ± 1
H	296 ± 3*	299 ± 5*	294 ± 3*	289 ± 1*
T	300 ± 3*	301 ± 6*	310 ± 2*,**	307 ± 2*,**
Oncotic pressure (mmHg)				
C	18.5 ± 0.5	17.2 ± 1.9	16.6 ± 0.3	15.7 ± 0.8
H	14.5 ± 0.9*	14.7 ± 1.3*	13.2 ± 0.6*	12.5 ± 0.8*
T	13.8 ± 0.9*	16.9 ± 1.6	10.9 ± 0.3*,**	12.4 ± 0.7*
Protein (g/dl)				
C	6.7 ± 0.1	5.9 ± 0.1	6.0 ± 0.1	5.6 ± 0.2
H	6.0 ± 0.2*	5.4 ± 0.2	5.2 ± 0.2*	4.9 ± 0.2*
T	5.8 ± 0.2*	5.2 ± 0.2*	4.5 ± 0.1*,**	4.3 ± 0.1*,**
Hematocrit (%)				
C	33 ± 2	33 ± 1	33 ± 1	31 ± 1
H	26 ± 2*	25 ± 1*	24 ± 1*	22 ± 1*
T	25 ± 2*	22 ± 1*,**	20 ± 1*,**	18 ± 1*,**
Hemoglobin				
C	9.9 ± 0.7	10.3 ± 0.3	9.9 ± 0.4	9.3 ± 0.5
H	7.5 ± 0.5*	7.5 ± 0.4*	8.0 ± 0.3*	6.7 ± 0.4*
T	7.0 ± 0.4*	6.4 ± 0.3*,**	6.6 ± 0.3*,**	5.3 ± 0.3*,**

[a]NS = normal saline ("isotonic" in text).
[b]D = dextran.
[c]HS = hypertonic saline.
[d]HSD = hypertonic saline/dextran.
*Significantly different from C ($P < 0.05$).
**Significantly different from H ($P < 0.05$).

to increase survival. Although Maningas et al. [12] also employed conscious swine, differences in survival may be attributed to a variety of factors: they used a different hemorrhage procedure (46 ml/kg over 15 min compared to our 37.5 ml/kg over 60 min); their animals were neither splenectomized nor restrained in a Pavlov sling as in our study; and they used a greater volume of resuscitation solution (11.5 ml/kg compared to our 4 ml/kg). Procedural disparities also may explain some of the functional differences seen in these two studies as well as those reported by others [5–11,13,15–17,23,24]. Nevertheless, all investigations have shown that treatment with small volumes of HSD significantly improves the functional status of animals subjected to severe hemorrhagic hypotension as compared to equal volumes of NS.

What functional changes could account for improved resuscitation following treatment with HSD compared to HS alone? One effect could be the restoration of cardiac function. Hypertonic saline/dextran produced a significantly greater increase

in cardiac output than HS alone; at the 5 min point after resuscitation, HSD was elevated to 114% of control levels, HS to 74%. This early response difference has not been observed in other investigations [11,13,14]. In contrast to our study, others [11,13,14] have shown a persistence of the increase in cardiac index after treatment, while we observed a decrease 60 min after treatment. The reduced value at 60 min, although still greater than that observed at the end of hemorrhage, suggests that factors other than improved cardiac output may be contributing to survival.

In our study, heart rate was reduced after treatment with both hypertonic solutions. Therefore, tachycardia did not contribute to the improvement in cardiac index. An augmented stroke volume was the primary contributor, an effect that was consistent with results obtained in earlier studies of HSD [11,13,14] and HS alone [5,11]. The augmentation seen here and in other studies was due, presumably, to improved venous return and thus cardiac filling. These effects could be mediated by one or more of the following factors: a direct or indirect vasodilatory action of hypertonic sodium [6,10,25–31]; expansion of vascular volume [5,8,9,11,15], or a reduction in blood viscosity [32–35].

With respect to volume expansion, administration of HS has been shown to cause an osmotically induced redistribution of water from the extracellular to the intravascular space and thus to the vascular compartment, a consistent but transient effect [5,8,9,11,15]. The ultimate effect, an increased blood volume, presumably improves venous return, hence, cardiac output. The initial expansion of vascular volume, however, cannot account fully for the differential effects of HS and HSD seen in our study. As judged from hematocrit changes following resuscitation, the increase in volume was similar after administering both solutions, yet the increase in cardiac index was significantly greater after HSD treatment than after HS treatment. The presence of D, however, could have enhanced survival because the cardiac output of the HSD treated pigs did not revert to post-hemorrhage levels during the course of recovery as it did in the pigs treated with HS alone. This beneficial effect appeared attributable to the maintenance of an improved vascular volume by the oncotic action of D; subsequent to an initial resuscitation decrement, hematocrit values gradually rise in pigs that receive hypertonic saline alone but not in pigs receiving HSD (unpublished data).

We interpret the improvement in venous return, and thus cardiac index, after administration of the HSD solution as attributable to the following factors: increased vascular volume, reduced venous capacity, and reduced blood viscosity. These changes do not result in adequate improvement in venous return sufficient to sustain cardiac index and consequently life when HS or D are administered alone. Nevertheless, the combination of these solutions in the form of HSD does. The effects elicited by HS and D alone could be additive, resulting in the effective combination solution. Accordingly, the increase in cardiac index, and presumably venous return, was 74% ± 16% with HS alone and with D 33% ± 17%. HSD produced a 118% ± 22% increase, a value consistent with an additive effect.

In summary, small-volume resuscitation with 4 ml/kg of HSD solution improves short-term survival following hemorrhagic hypovolemia in conscious immature swine by increasing cardiac output, the latter effect being entirely attributable to an elevation of stroke volume index. The increase in stroke volume index is facilitated by a variety of factors (expansion of plasma volume, vasodilation, reduced peripheral vasculature, reduced venous capacity, reduced blood viscosity,

and reduced flow impedance in the microvasculature). Detrimental effects of HSD resuscitation were negligible in our study of conscious swine subjected to a normally lethal fixed-volume hemorrhage.

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The experiments described in this paper were performed in adherence to the NIH guidelines for the use of experimental animals.