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**RESUSCITATION FROM HYPOVOLEMIA IN SWINE
WITH INTRAOSSEOUS INFUSION OF A SATURATED
SALT-DEXTRAN SOLUTION (SSD)**

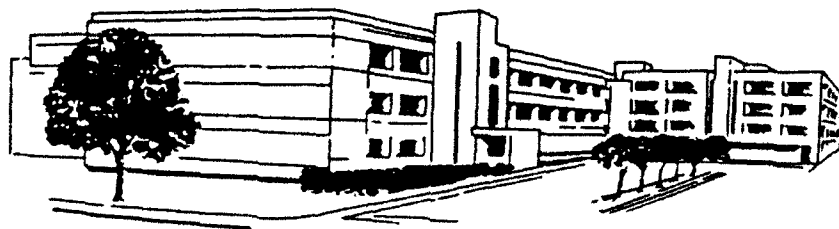
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and G.C. Kramer**

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Division of Military Trauma Research

October 1992



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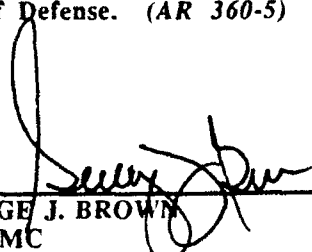
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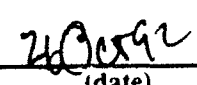
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In addition, cardiac output was better sustained after 2 hrs with SSD than with NS (4.9 ± 0.2 vs. 3.8 ± 0.3 L/min). No deleterious effects of IO infusion of SSD were observed, although mean plasma sodium concentrations reached 154 ± 2 mEq/L. From the improvement in cardiovascular parameters and the lack of significant sternal or pulmonary pathology, these data suggest that IO infusion of SSD can effectively treat hypovolemia and may allow field treatment when logistic considerations make conventional resuscitation impractical.

ABSTRACT

Prehospital fluid resuscitation of traumatic injury is limited by difficulty in delivering large volumes of fluid in the field and time delays associated with gaining vascular access. We addressed these limitations in 14 anesthetized swine by evaluating a highly efficient volume expander, a near saturated salt-dextran solution (SSD) administered through a new device which gains vascular access via intraosseous (IO) infusion into the sternal bone marrow. After a steady state baseline, all animals were hemorrhaged to 45 mmHg for one hr. Half of the hemorrhaged animals were then treated with a 10-30 minute IO infusion of either normal saline (NS) or SSD until cardiac output was restored to baseline. No further infusion was given and animals were monitored for 2 hrs. Both regimens were able to restore cardiac output to baseline, but only 1.3 ± 0.1 mL/kg of SSD was required vs. 31.6 ± 6.3 mL/kg for NS. In addition, cardiac output was better sustained after 2 hrs with SSD than with NS (4.9 ± 0.2 vs. 3.8 ± 0.3 L/min). No deleterious effects of IO infusion of SSD were observed, although mean plasma sodium concentrations reached 154 ± 2 mEq/L. From the improvement in cardiovascular parameters and the lack of significant sternal or pulmonary pathology, these data suggest that IO infusion of SSD can effectively treat hypovolemia and may allow field treatment when logistic considerations make conventional resuscitation impractical.

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**Resuscitation From Hypovolemia in Swine with
Intraosseous Infusion of a Saturated Salt-Dextran
Solution (SSD) -- D. Runyon, S. Bruttig, M. Dubick,
C. Clifford, G. Kramer.**

INTRODUCTION

Current methods of prehospital treatment of hemorrhagic shock in both civilians and military combat casualties are often ineffective. Two major limitations of field resuscitation of hemorrhage are the logistical difficulties associated with administering the large volumes needed for vascular expansion after severe hemorrhage and the time delays/failure rates associated with vascular access.

It has long been known that intraosseous (IO) infusion directly into red marrow is a rapid and reliable means of gaining vascular access (1,2). In children and infants, all bones contain red marrow and the proximal tibia is often used for emergency vascular access (3-5). In adults, however, avascular yellow marrow replaces the red marrow of the tibia, therefore, the sternum has most often been used for IO infusion of fluid, blood and drugs (1). Unfortunately, the tortuous red marrow presents substantial hydraulic resistance and rapid infusion rates are unachievable, precluding prompt resuscitation of shock using conventional large volume therapy (6).

An alternative to conventional resuscitation solutions is highly concentrated crystalloid-colloid mixtures shown effective in exceedingly small volumes for the treatment of circulatory shock. Recent resuscitation research evaluating the use of 7.5% NaCl/6% Dextran-70 (HSD), has shown it to be effective in volumes equal to only one-tenth that of the hemorrhaged volume, whether administered IV or IO (7-9). These solutions have also shown efficacy in selected populations of trauma patients when infused in a standard dose of 250 mL (10-12). An ultra small volume (1 mL/kg) formulation of near saturated 25% NaCl/24% Dextran-70 (SSD) has recently been suggested for military use, delivering the same NaCl-dextran load as HSD, but in a smaller volume (13,14). If proven safe and effective, this solution could potentially

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further reduce volume requirements for resuscitation to a single syringe of 100 mL or less. Likewise, this small volume could be administered IO in a timely manner. Thus, the present study evaluated resuscitation from hemorrhagic hypovolemia in swine using IO infusion of SSD and compared the results with IO infusion of normal saline (NS).

MATERIALS AND METHODS

Animal Preparation:

Experiments were performed on 14 immature, splenectomized male Duroc pigs obtained from UC Davis. Pigs weighed 44.9 ± 1.8 kg, and were randomly assigned to two treatment groups of seven animals each. Animals were fed a standard diet, observed for at least two weeks to ensure a good state of health, and fasted overnight before experimentation. Pre-anesthesia was induced with ketamine HCl (2 mg/kg), xylazine HCl (2 mg/kg), and atropine (0.1 mg/kg), tracheal intubation was performed and anesthesia was maintained with isoflurane (1-2%), nitrous oxide (50%) and oxygen (50%). Artificial ventilation using a time-cycled ventilator (Unitrol Ventilator, Ohio Medical Products, Madison, WI) was started using a tidal volume of 10-12 mL/kg and adjusted to maintain PaCO₂ within normal physiologic levels throughout the experiment. The pig model was chosen because of the similarity in the response of swine and humans to hemorrhage (15), while the anesthetic agent was selected for its ability to maintain cardiovascular stability in pigs (16).

Surgical Procedures:

After placement of the animal in a supine position, vascular catheters were inserted into the thoracic aorta via the left carotid artery and into the abdominal aorta via the right femoral artery. A balloon-tipped 7.5F Swan-Ganz thermodilution catheter was positioned in the pulmonary artery via the left internal jugular vein to measure pressures and cardiac output. Catheter placements were determined by pressure tracings and confirmed at the end of the experiment by inspection. The catheters were connected

to P23 Db pressure transducers, then connected to a Gould ES-2000 multi-channel monitor and recorder for continuous monitoring of aortic, pulmonary artery and central venous pressures. All catheters were continuously flushed with a heparinized 0.9% NaCl solution (1 mL/hr) to assure patency. Ultrasonic flow probes (Model T 101, Transonics Systems, Ithaca, NY) were placed on the portal vein and left femoral artery. Throughout the surgical procedure, each animal received about 1500 mL of warm 37°C 0.9% saline to maintain hydration and pressures and was covered with an electric blanket adjusted to maintain normal body temperature.

Experimental Protocol:

Each experiment consisted of 1 hr of baseline observation after the completion of surgery, followed by 1 hr of hypovolemic hypotension and a 2 hr resuscitation period. After the initial 1 hr of baseline measurements, blood was removed over a 15 min period through the femoral artery catheter until mean arterial pressure was reduced to 45 mmHg and maintained for the remainder of the hour with additional bleeding as needed. No shed blood was reinfused at any time. The IO vascular access device was inserted into the sternum and resuscitation was accomplished by infusing fluid over 10-30 min (normal saline, NS; or saturated salt dextran, SSD) (17). The goal of each resuscitation fluid was to restore cardiac output to baseline. Using NS, this required hand pressurized delivery of a large volume infused as rapidly as possible (generally over a 10-30 min time period) to restore cardiac output. SSD resuscitation was accomplished with substantially smaller volumes, and therefore, could have been infused in a shorter time period. However, by experimental design the infusion times for SSD infusion were paired with an NS experiment such that the total infusion time was the same for each solution. This permitted a direct comparison of isotonic and hypertonic resuscitation to the same physiological endpoint and over the same time course.

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Measured Variables:

Hemodynamic variables were measured every 30 min during the baseline period, every 15 min during hemorrhage and at 2, 5, 15, 30, 45, 60, 90, and 120 min during resuscitation. The following measured events were recorded: mean systemic arterial pressure (MAP), mean pulmonary arterial pressure (PAP), pulmonary wedge pressure (PWP), central venous pressure (CVP), cardiac output (CO), heart rate (HR), portal vein, and femoral artery blood flows. Arterial and venous blood gases were measured at 30 min intervals throughout the experiment (Instrumentation Laboratory System 1320, Instrumentation Labs., Lexington, MA) to adjust the ventilator parameters and maintain normal levels of PaCO_2 . Blood samples were collected at the times that hemodynamic variables were measured during baseline, hemorrhage, and resuscitation. Hematocrit was determined and levels of sodium, potassium, chloride, lactate, and total protein were analyzed in plasma using standard laboratory methods by the Analytical Chemistry Branch, Letterman Army Institute of Research. Plasma dextran concentrations were determined by the method of Roe (18) as previously detailed (19). Plasma free hemoglobin concentrations were determined by the method described by Fairbanks and Klee (20).

Calculated Variables:

Hemodynamic variables were calculated by means of commonly used formulas. Calculated variables include total peripheral resistance and relative changes in vascular resistance of skin, muscle hindlimb and portal circulatory beds. Blood volume expansion (BVexp) following resuscitation was calculated from the changes in hematocrit in the splenectomized animals using the formula $\text{BVexp} = (\text{Hct}_s - \text{Hct}_r) / \text{Hct}_r \times 100$, where Hct_s and Hct_r are the hematocrits at the end of hemorrhage and at the times after resuscitation, respectively (21).

Pathology:

After the last physiological measurement, each animal was euthanized with a saturated potassium chloride solution. Animals were examined for gross

pathology associated with the experimental preparation or IO infusion. Samples of the lung and sternum were fixed by immersion in 10% neutral buffered formalin, embedded in paraffin and prepared for histological evaluation of acute lesions, presence or absence of thrombi, fat or bone emboli, necrosis or hemorrhage to the lung, and decreased cellularity (washout) or hemorrhage in the bone marrow. Lesions observed were graded from 1 to 5 (minimal, mild, moderate, marked, severe). All slides were read by a veterinary pathologist who was blinded to the treatment.

Statistical Analysis:

The hemodynamic data and the measured and calculated variables were statistically analyzed by one-way analysis of variance to compare baseline and hemorrhage periods for each group. Significant differences between the two resuscitation regimens were determined using a 2-way analysis of covariance model, with factors group (NS and SSD) taken as a fixed effect, and time taken as a repeated measurement (22). The last hemorrhage measurement before infusion was used as a covariate. If a significant F statistic was observed ($p < 0.05$), the Newman-Keuls method of multiple comparison was used to determine which groups were different. Pathology observations were subjectively evaluated.

RESULTS

Hemodynamics:

Mean arterial pressure (MAP) was reduced and maintained near 45 mmHg (Fig 1a) during the hemorrhage period after bleeding 700.7 ± 51.7 mL blood in the NS group and 795.7 ± 93.1 mL blood in the SSD group. There were no statistically significant differences in hemodynamic variables between the NS and SSD groups during baseline and hemorrhage periods. Animals were resuscitated to their respective baseline cardiac outputs (Fig 1b) using either NS or SSD. In both groups, MAP was briefly returned to near baseline levels at the end of infusion, but gradually decreased over the next 90 min (Fig 1a). MAP was not different

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following resuscitation between the groups. Baseline levels of cardiac output (CO) were achieved in both groups with the SSD group showing a slightly higher end-point immediately after resuscitation that persisted throughout the remainder of the experiment (Fig 1b). SSD resuscitation was better able to sustain CO at baseline levels throughout the post-resuscitation period than NS resuscitation.

Heart rate (HR) increased during hemorrhage to 172 ± 19 and 162 ± 21 beats/min in the NS and SSD groups, respectively (Fig 2a). Five min after the initiation of fluid infusion, HR had decreased significantly, but was still comparable between groups. However, by 30 min after infusion, HR between the two groups was significantly different. HR in the NS group dropped to baseline and then slowly returned to hemorrhage levels by the end of the experiment. In contrast, the SSD group showed a slight decrease in HR to 144 ± 20 beats/min after SSD infusion, which was maintained for the duration of the experiment.

Stroke volume (SV) was similar between the two groups during the baseline and hemorrhage periods. Hemorrhage decreased SV in both groups (Fig 2b). Infusion of NS or SSD returned SV back to baseline levels. Both groups had similar responses in SV until the end of the experiment where SSD was able to maintain SV at a statistically higher level than NS ($p < 0.05$).

Systemic vascular resistance (SVR) increased in both groups with hemorrhage and then fell dramatically with the onset of resuscitation (Fig 3a). The SVR in the NS group decreased to baseline levels which were maintained throughout the experiment. The SSD group showed a greater fall in SVR to below baseline with resuscitation, an effect maintained for the duration of the experiments. Differences between groups were statistically significant during resuscitation and at the end of the experiment.

Maximum blood volume expansion, based on changes in hematocrit, was 47% and 43% in the NS and SSD groups, respectively, 15 min after initiation of

resuscitation (Fig 3b; Table 1). In the NS group 60 min into the resuscitation period, the blood volume decreased to about 126% of the initial blood volume and was about 18% expanded at 120 min. In contrast, in the SSD group, blood volume remained about 138% of the initial value throughout the 2 hr experimental period. In addition, it was calculated that blood volume was expanded over 5 mL for each mL of SSD infused, whereas NS expanded blood volume only 0.3 mL for each mL infused.

Cardiac preload and output are compared in Fig 4. Plots of cardiac output vs. pulmonary wedge pressure (PWP) are shown at the end of hemorrhage and at 15 min after resuscitation in each group. The NS group had a PWP of 4.7 ± 1.1 mmHg and a cardiac output of 3.0 ± 0.4 L/min at the end of hemorrhage. Both of these values increased (PWP to 7.86 ± 1.3 mmHg and CO to 5.3 ± 0.5 L/min) by 15 min post-resuscitation. The SSD group had a PWP of 4.4 ± 1.6 mmHg and a CO of 2.8 ± 0.3 L/min at the end of hemorrhage. By 15 min post-resuscitation, the CO had risen to 6.2 ± 0.3 L/min while the PWP remained relatively unchanged (4.7 ± 1.4).

Blood Flows:

Ultrasonic Doppler flow probes were used to measure flow rates in the portal vein and the right femoral artery (Table 2). The blood flow through the femoral artery and the portal vein was similar between groups during baseline and hemorrhage. By the end of hemorrhage, flow in both vessels had decreased markedly. The portal vein blood flow fell 62% to 70%, while femoral artery blood flow decreased 42% to 57% by the end of hemorrhage. Resuscitation initially improved portal blood flow to near baseline levels in both groups. The flow, however, was not sustained with NS resuscitation and rapidly fell, reaching hemorrhaged levels by the end of the experiment. After SSD resuscitation, portal flow was sustained significantly higher than in the NS group ($p < 0.05$) for the duration of the experiment. Femoral artery blood flows were also increased with resuscitation in both groups, but not to baseline, and with no significant difference

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between groups. The slight improvement in femoral artery blood flow in both groups was only transient.

Blood Composition:

Hemorrhage of the pigs resulted in a similar fall in hematocrit (Hct) in both groups (Table 1). Resuscitation with fluids resulted in a marked fall in Hct from the hemorrhaged value of 29.1 ± 1.4 to 21.6 ± 0.8 (NS) and 28.1 ± 1.0 to 22.3 ± 1.1 (SSD). The NS group Hct rose steadily after completion of fluid administration. In the SSD group, however, Hct stayed at the same level throughout the post-resuscitation period. The difference from the NS group was statistically significant at 2 hr after infusion. In addition, changes in plasma lactate concentrations following hemorrhage and resuscitation were similar in both groups (Table 1). SSD infusion resulted in a transient increase in plasma free hemoglobin concentrations over the first 60 min in comparison to the NS group (Table 1), but the concentrations were not clinically significant.

Fluid And Electrolyte Balance:

The amount of blood withdrawn from each group was similar. The NS group, however required significantly more infused fluid in order to achieve the target physiologic endpoint of baseline cardiac output (Fig 5). The NS group required 1363.9 ± 261.2 mL of fluid compared to 58.8 ± 4.7 mL of SSD or 31.6 ± 6.3 mL/kg vs. 1.3 ± 0.1 mL/kg, respectively.

Plasma sodium concentrations stayed constant in both groups throughout the baseline and hemorrhage periods (Table 3). Infusion of NS caused no significant change in plasma sodium. The SSD infusion caused a significant rise in sodium concentrations to a maximum of 154 ± 2 mEq/L, which then decreased to 147 ± 1 mEq/L for the duration of the experiment. Plasma potassium concentrations were similar between groups at baseline, and increased to 5.0 ± 0.2 and 5.7 ± 0.3 mEq/L in the NS and SSD groups, respectively, during hemorrhage (Table 3). Resuscitation decreased the potassium concentration to near baseline values in the NS group.

Although plasma potassium concentrations were slightly higher in the SSD than in the NS groups following resuscitation, the differences were not statistically significant. Plasma chloride concentrations were also elevated by SSD administration, and plasma chloride peaked with plasma sodium (Table 3). The values, however, did not achieve statistical significance in comparison to baseline or the NS group.

Pathology:

Table 4 summarized the histological observations of 5 pigs in the NS group and 6 pigs in the SSD group. Both groups had a similarly low incidence of pulmonary thrombosis, a finding that is normally associated with the use of venous and pulmonary catheters in this animal preparation. There were 2 minimal to mild cases of vasculitis in the NS group and none in the SSD group. The NS group showed only 2 cases with minimal to mild pulmonary thrombi of the 5 examined. The NS infused pigs showed no signs of pulmonary vasculitis or sternal thrombi. Alterations in the sternal marrow were similar in both groups and included acute hemorrhage at the site of needle insertion and a washout of marrow cells. There was a greater amount and severity of acute hemorrhage and washout in the NS group as compared with the SSD group. The SSD group displayed 2 cases with pulmonary vasculitis and 1 case with sternal thrombi, but these instances were minimal to mild. These pathological changes were not unexpected and indicated no major pathological consequences following IO infusions.

DISCUSSION

Achieving rapid vascular access in the field may be compromised by severe hemorrhage due to circulatory collapse (1-5). Many investigators have reported that obtaining an IV line can require more than 10 min with failure to get access commonplace. To circumvent this difficulty, IO infusion, particularly in children, was introduced to deliver drugs and other solutions. Previous studies using IO infusion of various drugs have reported rapid distribution of the infused substance throughout the general circulation

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(1,2,23,24). Early studies by Tocantins, et al. (2) showed that a dye solution infused in the sternum enters the right heart very quickly. Thus, the red marrow of bone provides a virtual non-collapsible vein.

The current standard of treatment of hemorrhagic hypotension consists of infusing large amounts of isotonic fluid into the vasculature. This, however, can be impossible, especially if IV lines are unobtainable. The IO route of infusion is an alternative method, but the hydraulic resistance of bone marrow has been shown to limit rates at which fluids can be infused (13). In their studies of IO infusion of Ringer's lactate to treat hypovolemia in dogs, Hodge et al. (25) suggested that because flow was limited and large volumes of fluid are required, sufficient flow rates for adequate and prompt resuscitation of hemorrhagic shock were unattainable. To reduce fluid requirements, many investigators have reported the use of hypertonic fluids (26,27). Newer hypertonic/hyperoncotic agents have been shown to minimize the amounts of fluid given, stimulate cardiac function, cause arteriole vasodilation and also produce a profound plasma volume expansion (28-30). Wade et al. (7) and Maningas et al. (8) have reported that a dose as small as 4 mL/kg of 7.5% NaCl/6% Dextran-70 (HSD) is sufficient to resuscitate a potentially fatally hemorrhaged pig. Thus, the reduced volume requirements for HSD (7,19,31) make it a potentially useful fluid for IO infusion. Recently, Chavez-Negrete, et al. (32,33) used the adult sternum as the site for emergency infusion with 250 ml of HSD. Emergency room treatment of patients who were hypotensive from gastrointestinal bleeding was more effective with IO infusion of HSD than with IV infusion of crystalloids and blood (33). A third group treated with HSD IV had a similar outcome to those infused IO. Also, Dubick, et al. (34) recently demonstrated that infusion times for sternal administration of HSD can be short, suggesting that small volume IO infusions can be administered as rapidly as IV infusions.

In an attempt to further reduce the fluid requirements and thus increase the speed and efficiency with which fluid can be infused, the present study

investigated resuscitation with a saturated salt-dextran solution. This 25% NaCl/24% Dextran-70 (SSD) can decrease the fluid requirements from 4 mL/kg for HSD to about 1 mL/kg, yet deliver the same solute load. With infusion amounts this small, it is relatively simple to give a single dose of SSD via an intraosseous device to achieve full and rapid normalization of cardiovascular function. The rapid rise in plasma Na and dextran following IO infusion of SSD in the present study is consistent with previous studies with HSD. Dubick et al. (34) indicated that IO infusion of HSD resulted in rapid vascular entry of Na and dextran, such that plasma Na and dextran concentrations peaked by the end of infusion or within a minute thereafter. In addition, calculation of the estimated vascular dextran suggested complete delivery into the vasculature of the dextran infused IO.

The three main and unique physiological mechanisms of hypertonic resuscitation are clearly illustrated in the present experiments. First, hypertonic fluids are believed to produce a rapid plasma volume expansion by pulling fluids from the extracellular space into the vasculature. As indicated by blood volume measurements and hematocrit in the present study, SSD sustained an elevated blood volume throughout the experiment while NS did not.

Secondly, hypertonic fluids have been shown to exert a direct inotropic effect on the heart (35,36). In the present study these actions were most clearly illustrated by SSD increasing cardiac output without a concomitant increase in filling pressure. This suggests that hypertonic resuscitation caused a shift to a higher Starling cardiac function curve. This is contrasted with NS resuscitation in which increased cardiac output was associated with increased filling pressure. Similar observations following HSD therapy have also been previously described by Pascual, et al. (37).

The third mechanism of hypertonic fluids is believed to be vasodilation of the arterioles. In the present study a reduction in systemic vascular resistance was observed in both the NS and SSD groups.

The SSD group, however, produced a substantially lower resistance which was maintained. This may be due to a direct osmotic effect on the smooth muscle of the arterioles. Of interest is the apparent preferential redistribution of the cardiac output. Blood flow was reduced to both the gut (portal vein) and the peripheral skin and muscle (femoral artery) during hemorrhage. With both NS and SSD resuscitation, blood flows increased, but not to baseline levels suggesting that a redistribution of cardiac output to more vital organs occurred, since cardiac output was restored to baseline. These data also suggest that SSD resuscitation preferentially maintained blood to the gut better than NS. During the resuscitation period the mean portal blood flow in the SSD group ranged from 69-84% of baseline, while it tended to be substantially lower (45-63% of baseline) in the NS group. An apparent, opposite trend was seen in the femoral artery where blood flows in the NS group tended to be higher. A redistribution away from skin and skeletal muscle toward the mesenteric circulation has been previously reported with hypertonic saline after hemorrhagic shock in dogs (14). A recent study has suggested the ability of HSD resuscitation to maintain gut mucosal blood flow better than conventional therapy (38).

Previous studies have raised concern over infusion of hypertonic saline solutions with Na concentrations equal to or exceeding 15%, particularly with respect to the potential for red cell hemolysis. Rocha e Silva et al. (14) reported marked increases in plasma free hemoglobin following infusion of 15% NaCl in dogs. However, in the present study using SSD in pigs, or in recent studies with sheep (13,39), infusion of SSD or NaCl, alone, or in concentrations as high as 25%, caused no clinically significant increases in plasma free hemoglobin. It is unknown if the low level of hemolysis in the present study relates to the IO route, slow rates of infusion, or other factors. Although these data suggest that dog blood may be more sensitive to hypertonic NaCl solutions than pigs or sheep, the sensitivity of human blood after similar hypertonic infusions remains to be established.

Another concern is the potential pathology associated with IO infusions. A number of adverse reactions have been reported following IO infusion into both the tibia and the sternum (1,40), yet the complication rate of IO infusion appears no greater than that of IV infusion. There have been a few cases of focal hemorrhage, washout and infiltration, a very few cases of fat emboli, and rarely a case of osteomyelitis as a result of the IO infusion (1,5,40,41). These data suggest that aseptic techniques are practical and effective for IO infusions. The only feature that is consistently reported with IO infusion is washout in the area immediately surrounding the site of infusion. This area did not extend to other areas of the marrow. Also, the bone heals relatively quickly and is restored to normal in a short time. These observations have been recently supported by the report of Dedrick et al. (42) following tibial IO infusions of NS or hypertonic sodium bicarbonate. Intraosseous infusions of either isotonic or hypertonic solutions do not appear to be more dangerous than intravenous or intramuscular infusions. The use of the IO infusion device employed in the present study has been designed to greatly diminish the adverse effects described above (9,17).

The potential clinical advantages of SSD compared to other hypertonic solutions may be predominantly logistic rather than physiologic. In a direct comparison between SSD and HSD and NS in which all were continuously infused as needed to maintain baseline cardiac outputs for 2 hr following intraoperative hypovolemia, the final volume requirements of each solution were 1.2, 4, and 120 mL/kg, respectively (37). This equates to 84 mL for SSD versus 250 mL for HSD and 8.4 L for NS in a 70 kg patient. This volume saving of both hypotonic fluids compared to NS is significant and offers a means for timely prehospital resuscitation. The volume savings between SSD and HSD is probably of little consequence in civilian trauma, but may be of major consequence in military trauma. A single syringe dose of SSD could resuscitate a major blood loss, allowing the corpsmen to carry many life-saving doses into the field. Therefore, the data from the present study suggest that IO infusion of SSD can effectively

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resuscitate from hypovolemia and may be a viable alternative when vascular access is compromised or logistical considerations make conventional resuscitation impractical.

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REFERENCES

1. Tocantins LM, O'Neill JF, Price AH. Infusions of blood and other fluids via the bone marrow in traumatic shock and other forms of peripheral circulatory failure, *Ann. Surg.* 114 (1941) 1085-1092.
2. Tocantins LM. Rapid absorption of substances injected into the bone marrow. *Proc. Soc. Exp. Biol. Med.* 45 (1940) 292-296.
3. Fiser DH. Intraosseous infusion. *N. Engl. J. Med.* 322 (1990), 1579-1581.
4. Hodge D. Intraosseous infusions, A review. *Ped. Emerg. Care.* 1 (1985) 215-218.
5. McNamara RM, Spivey WH, Sussman C. Pediatric resuscitation without an intravenous line. *Am. J. Emerg. Med.* 4 (1986) 31-33.
6. Watson JC, Pascual J, Runyon DE, Kramer GC, Wisner DH. Intraosseous resuscitation from hemorrhage: Restoration of cardiac output using normal saline (NS) and 7.5% hypertonic saline 6% dextran (HSD). *Circ. Shock* 31 (1990) 60.
7. Wade CE, Hannon JP, Bossone CA, Hunt MM, Loveday JA, Coppes R, Gildengorin VL. Resuscitation of conscious pigs following hemorrhage: Comparative efficacy of small-volume resuscitation. *Circ. Shock*, 29 (1989) 193-204.
8. Maningas PA. Resuscitation with 7.5% NaCl in 6% dextran 70 during hemorrhagic shock in swine. *Crit. Care Med.* 15 (1987) 1121-1126.
9. Halvorsen L, Bay BK, Perron PR, Gunther RA, Holcroft JW, Blaisdell FW, Kramer GC. Evaluation of an intraosseous infusion device for the resuscitation of hypovolemic shock. *J. Trauma* 30 (1990) 652-659.

10. Holcroft JW, Vassar MJ, Turner JE, Derlet RW, Kramer GC. 3% NaCl and 7.5% NaCl/Dextran 70 in the resuscitation of severely injured patients. *Ann. Surg.* 206 (1987) 279-288.
11. Mattox KL, Maningas PA, Moore EE, Mateer JR, Marx JA, Aprahamian C, Burch JM, Pepe PE. Prehospital hypertonic saline/dextran infusion for post-traumatic hypotension, The USA multicenter trial. *Ann. Surg.* 213 (1991) 482-491.
12. Vassar MJ, Perry CA, Gannaway WL, Holcroft JW. 7.5% sodium chloride/dextran for resuscitation of trauma patients undergoing helicopter transport. *Arch. Surg.* 126 (1991) 1065-1072.
13. Perron PR, Walsh JC, Gunther RA, Holcroft JW, Kramer GC. Resuscitation of hemorrhage (43 mL/kg) using less than 1 mL/kg of saturated NaCl/dextran solution. *Circ. Shock* 21 (1987) 321.
14. Rocha e Silva M, Velasco IT, Porfirio MF. Hypertonic saline resuscitation: Saturated salt-dextran solutions are equally effective, but induce hemolysis in dogs. *Crit. Care. Med.* 18 (1990) 203-207.
15. Hannon JP. Hemorrhage and hemorrhagic shock in swine, A review. *Inst. Rep. No. 449*, (1989) Presidio of San Francisco: Letterman Army Institute of Research.
16. Gross DR. Cardiovascular effects of inhalant anesthetic agents. In: *Animal Models in Cardiovascular Research*. Boston, Martinus Nijhoff Publisher, (1985) pp 244-300.
17. Bay BK, Henderson JM, Blaisdell FW, Kramer GC. A device for rapid vascular access to the sternal marrow spaces for delivery of resuscitation fluids. *Circ. Shock*, 27 (1989) 344-345.
18. Roe JH. The determination of dextran in blood and urine with anthrone reagent. *J. Biol. Chem.* 208 (1954) 889-896.

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19. Dubick MA, Summary JJ, Ryan BA, Wade CE. Dextran concentrations in plasma and urine following administration of 6% Dextran-70/7.5% NaCl to hemorrhaged and euvoletic conscious swine. *Circ. Shock* 29 (1989) 301-310.
20. Fairbanks VF, Klee GG. Biochemical aspects of hematology. In: *Textbook of Clinical Chemistry*. Editors: N.W. Tietz, W.B. Saunders and Co., Philadelphia, PA, 1986, pp 1534-1536.
21. Pascual JMS, Watson JC, Runyon DE, et al: Resuscitation of intraoperative hypovolemia: A comparison of normal saline and hyperosmotic/hyperoncotic solutions in swine. *Crit. Care Med.* 20 (1992) 200-210.
22. Remington RD, Schork MA. *Statistics with Applications to the Biological and Health Sciences*, Prentice Hall Inc., Englewood Cliffs; 1970.
23. Tocantins LM, O'Neill JF, Jones HW. Infusion of blood and other fluids via the bone marrow. *J. Am. Med. Assoc.* 117 (1941) 1229-1234.
24. Meyer LM, Perlmutter M. The absorption rate from the bone marrow. *J. Am. Med. Assoc.* 205 (1943) 187-190.
25. Hodge D III, Delagdo-Paredes C, Fleisher G. Intraosseous infusion flow rates in hypovolemic "pediatric" dogs. *Ann. Emerg. Med.* 16 (1987) 305-307.
26. Bitterman H, Triolo J, Lefer AM. Use of hypertonic saline in the treatment of hemorrhagic shock. *Circ. Shock*, 21 (1987) 271-283.
27. Nakayama S, Sibley L, Gunther RA, Holcroft JW, Kramer GC. Small-volume resuscitation with hypertonic saline (2,400 mOsm/liter) during hemorrhagic shock. *Circ. Shock*, 13 (1984) 149-159.

28. Wildenthal K, Mierzwiak DS, Mitchell JH. Acute effects of increased serum osmolality on left ventricular performance. *Am. J. Physiol.* 216 (1969) 898-904.
29. Gazitua S, Scott JB, Swindall B, Haddy FJ: Resistance responses to local changes in plasma osmolality in three vascular beds. *Am. J. Physiol.*, 220 (1971) 384-391.
30. Lopes OU, Velasco IT, Guertzenstein PG, Rocha e Silva M, Pontieri V. Hypertonic NaCl restores mean circulatory filling pressure in severely hypovolemic dogs. *Hypertension* 8 (suppl I), (1986) 1195-1199.
31. Maningas PA, Bellamy RF. Hypertonic sodium chloride solutions for the prehospital management of traumatic hemorrhagic shock: A possible improvement in the standard of care? *Ann. Emerg. Med.* 15 (1986) 1411-1414.
32. Chavez-Negrete A, Majluf S, Arguero R. Effectiveness of an intraosseous infusion of hypertonic saline dextran during the control of hypotension associated with brain death of organ donors. *Eur. Surg. Res.* 22 (1990) 313.
33. Chavez-Negrete A, Majluf Cruz S, Frati Munari A, Perches A, Arguero R. Treatment of hemorrhagic shock with intraosseous or intravenous infusion of hypertonic saline/dextran solution. *Eur. Surg. Res.* 23 (1991) 123-129.
34. Dubick MA, Runyon DE, Clifford CB, Kramer GC. Comparison of intraosseous and intravenous infusions of hypertonic saline dextran in swine. *Ann. Emerg. Med.* 20 (1991) 480.
35. Cross JS, Gruber DP, Burchard KW, Singh AK, Moran JM, Gann DS. Hypertonic saline fluid therapy following surgery: A prospective study. *J. Trauma*, 29 (1989) 817-826.

20-- Runyon et al.

36. Kien ND, Reitan JA, White DA, et al: Cardiac contractility and blood flow distribution following resuscitation with 7.5% hypertonic saline in anesthetized dogs. Circ. Shock 35 (1992) 109-116.
37. Pascual JMS, Runyon DE, Watson JC, Clifford CB, Dubick MA, Kramer GC. Resuscitation of hypovolemia in pigs using near saturated sodium chloride solution in dextran. Circ. Shock, in press.
38. Behrman SW, Fabian TC, Kudsk KA, Proctor KG. Microcirculatory flow changes after initial resuscitation of hemorrhagic shock with 7.5% hypertonic saline/6% Dextran 70. J. Trauma 31 (1991) 589-598.
39. Dubick MA, Summary JJ, Davis, JM, Greene JY, Wade CE, Kramer GC. Dose-response comparison between hyperosmotic saline (HS) and hyperoncotic Dextran-70 (HD) as plasma volume expanders. Circ. Shock 34 (1991) 37.
40. Tocantins LM, O'Neill JF. Complications of intraosseous therapy. Ann. Surg. 122 (1945) 266-277.
41. Kramer GC, Mertens SC, Halvorsen L, Holcroft JW, Perron PR, Gunther RA. Intraosseous infusion of hypertonic saline dextran: Effects on pulmonary function and the histology of the bone marrow. Circ. Shock 27 (1989) 348.
42. Dedrick DK, Mase C, Ranger W, et al: The effects of intraosseous infusion on the growth plate in a resting rabbit model. Ann. Emerg. Med. 21 (1992) 494-497.

TABLE 1
Effect of Hemorrhage and Resuscitation on Plasma Parameters¹

	Baseline	Post-Hemorrhage	Resuscitation period (min)				
			5	15	30	60	120
Hematocrit NS ² SSD ³	32.1±1.5	29.1±1.4	24.4±0.8	21.6±0.8	23.3±1.1	25.±0.9	27.0±1.5
	31.5±1.2	28.0±1.0	24.5±1.1	22.3±1.1	23.0±0.9	23.±1.2	23.3±1.5
Protein NS (g/dl) SSD	5.2±0.3	4.8±0.2	3.9±0.3	3.4±0.3	3.7±0.2	4.0±0.2	4.0±0.2
	5.2±0.2	4.8±0.2	4.6±0.2*	4.4±0.2*	4.5±0.2*	4.4±0.2	4.4±0.2
Lactate NS (mg/dl) SSD	14.8±1.7	29.1±4.6	—	37.3±6.0	34.1±6.3	30.2±6.3	29.0±6.6
	11.0±2.4	29.4±9.2	—	37.4±11.2	40.4±13.6	32.5±9.8	30.2±10.1
Free Hemoglobin NS (mg/dl) SSD	3.6±1.1	2.5±0.3	2.4±0.6	2.9±1.1	2.2±0.7	2.1±0.5	2.9±0.7
	4.0±1.2	5.3±1.2	6.3±2.5	9.0±2.4	6.8±0.9	5.9±1.5	2.8±0.5

¹Data expressed as mean ±S.E. for 7 animals/group.

²Normal Saline

³25% NaCl/24% Dextran-70

TABLE 2

Effects of SSD or NS Infusion on Portal Vein and Femoral Artery Blood Flow¹

	<u>Portal Vein²</u>		<u>Femoral Artery²</u>	
	<u>NS</u>	<u>SSD</u>	<u>NS</u>	<u>SSD</u>
Baseline	820±130	770±90	188±35	184±60
Post-Hemorrhage	250±40	290±60	80±39	108±39
Resuscitation				
5 min	360±40	410±70	99±41	107±36
15 min	700±90	660±60	123±46	123±33
30 min	520±70	650±70	119±39	106±27
60 min	490±60	640±70*	102±24	88±23
120 min	370±50	530±90*	98±26	68±26

¹Data expressed as mean ±S.E. for 7 animals/group²Blood flow units are mL/min

*p<0.05 from NS

TABLE 3

Effect of Hemorrhage and Resuscitation on Plasma Electrolytes and Dextran Concentrations¹

			Post- Hemorrhage	Resuscitation Period (min)				
				5	15	30	60	120
Sodium (mEq/L)	NS ²	Baseline	140±1	142±1	143±1	143±1	143±1	142±1
	SSD ³	142±1	141±1	153±3*	154±2*	152±2*	149±1*	149±1*
Potassium (mEq/L)	NS	4.5±0.1	5.0±0.2	4.2±0.2	3.9±0.2	4.1±0.1	4.5±0.2	4.9±0.2
	SSD	4.6±0.2	5.7±0.3	5.2±0.3	4.4±0.1	4.5±0.1	4.9±0.2	5.4±0.2
Chloride (mEq/L)	NS	110±3	111±2	114±3	114±2	113±3	112±2	109±2
	SSD	108±2	109±2	120±5	121±4	119±3	115±3	114±3
Dextran (mg/dl)	NS							
	SSD			229±51	407±64	465±55	402±46	391±44

¹Date expressed as mean ±S.E. from 7 animals/group²Normal Saline³25% NaCl/24% Dextran-70

*p<0.05 from group baseline

TABLE 4

Histological Observations Following IO Infusion of Either Normal
Saline or Saturated Salt Dextran¹

Treatment	Animal#	thrombosis	Lung vasculitis	acute hemor	washout	Sternum thrombus
NS ²	1	0/8	0/8	1/1 (3)	0/1	0/1
	2	2/5 (1)	0/5	2/2 (3)	2/2 (2)	0/2
	3	2/4 (2)	0/4	1/1 (3)	1/1 (2)	0/1
	4	0/3	0/3	1/1 (2)	1/1 (1)	0/1
	5	0/5	0/5	2/2 (3)	2/2 (2)	0/2
SSD ³	1	0/3	0/3	2/6 (2)	0/6	0/6
	2	0/5	0/5	1/2 (1)	0/2	1/2 (1)
	3	2/10 (2)	1/10 (2)	1/2 (2)	0/2	0/2
	4	1/4 (1)	2/4 (2)	0/2	1/2 (1)	0/2
	5	0/3	0/3	1/1 (2)	1/1 (1)	0/1
	6	0/3	0/3	1/1 (2)	1/1 (2)	0/1

¹Data represents the number of sections with thrombi or emboli out of the number of section examined. The number in parentheses is the severity grade where 0=no lesion; 1=minimal; 2=mild; 3=moderate; 4=marked; 5=severe.

²Normal Saline

³25% NaCl/24% Dextran 70

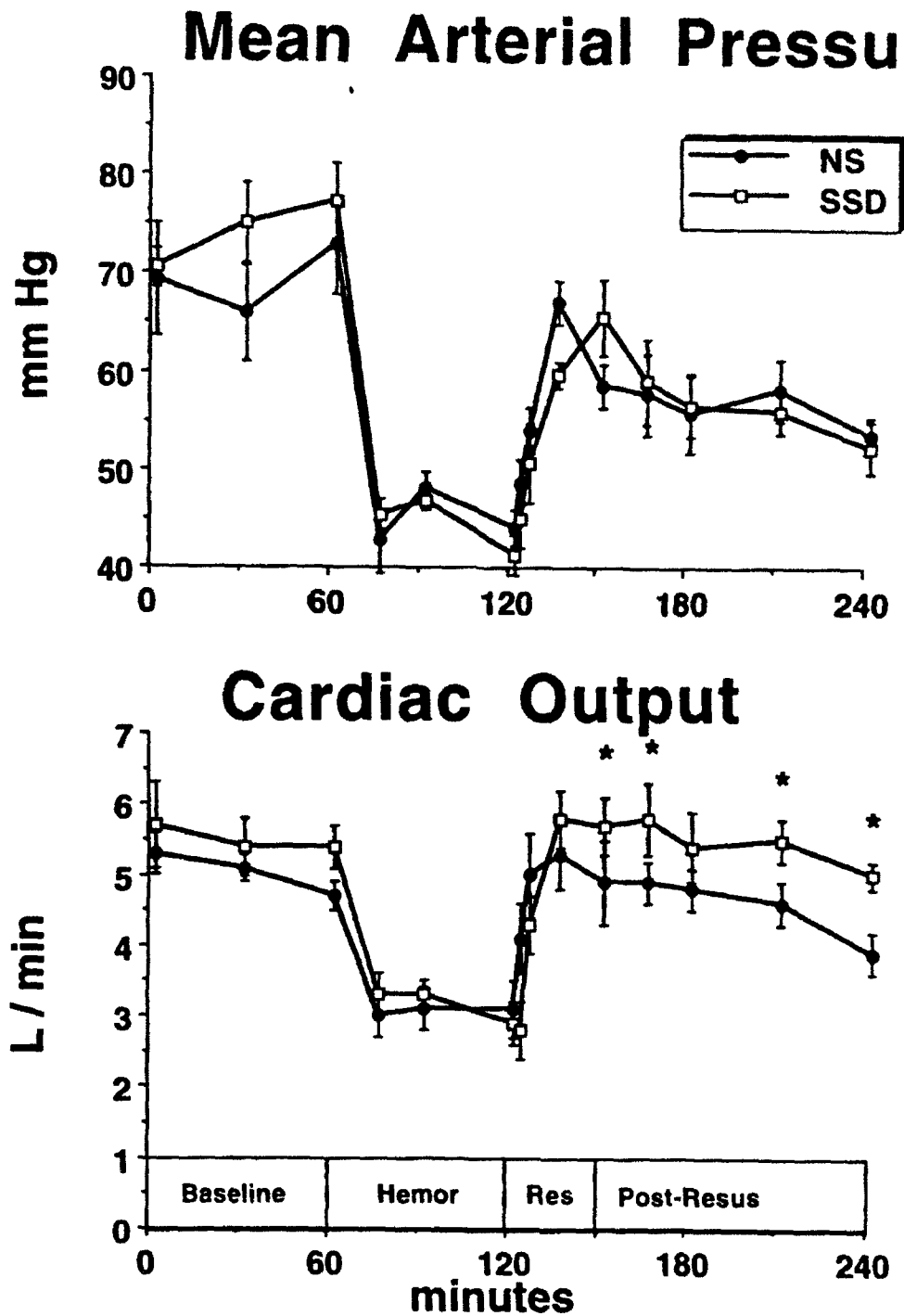


Fig 1: Mean arterial pressure (A) and Cardiac output (B) in hemorrhaged swine infused with normal saline (NS) or saturated salt dextran (SSD). Data represent mean $\pm$ S.E. of 7 animals/group.

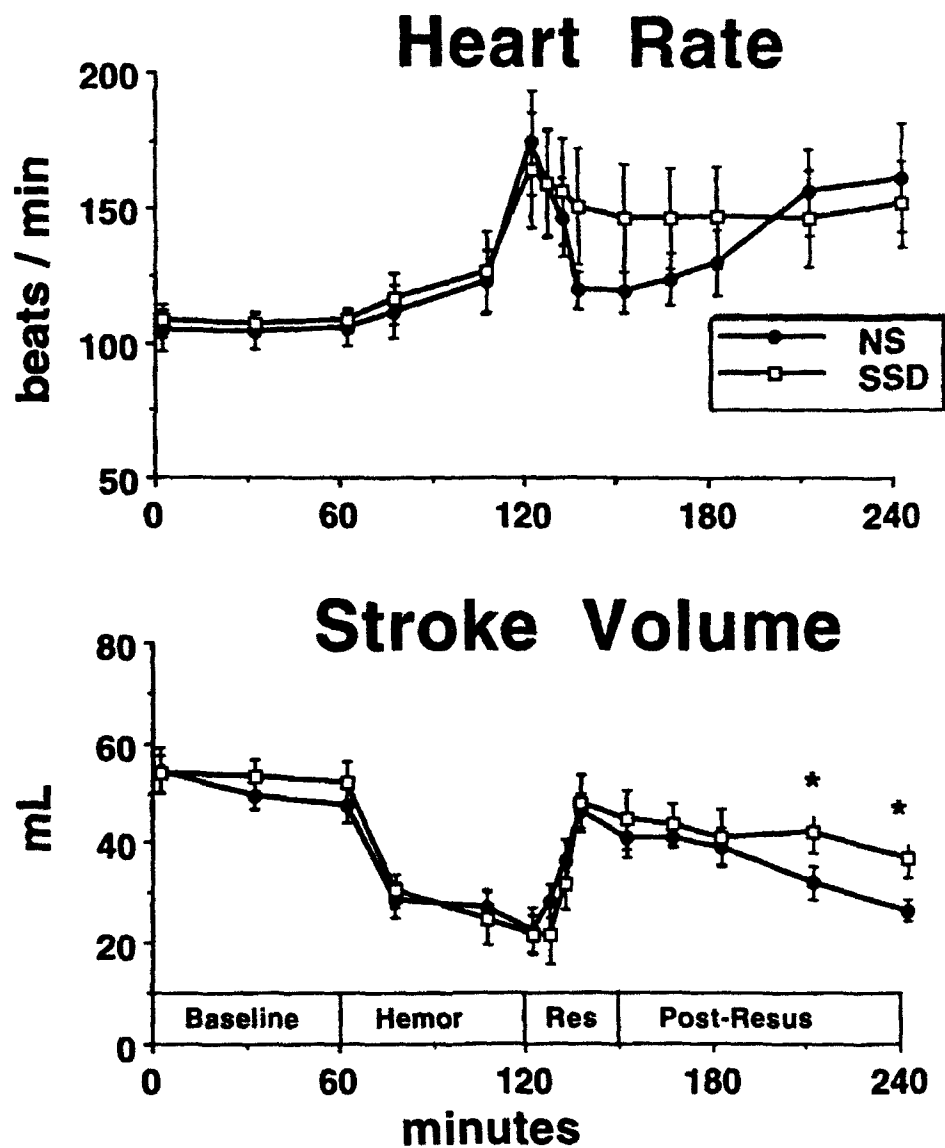


Fig 2: Heart rate (A) and stroke volume (B) in hemorrhaged swine infused with NS or SSD. Data expressed as mean $\pm$ S.E. of 7 animals/group.

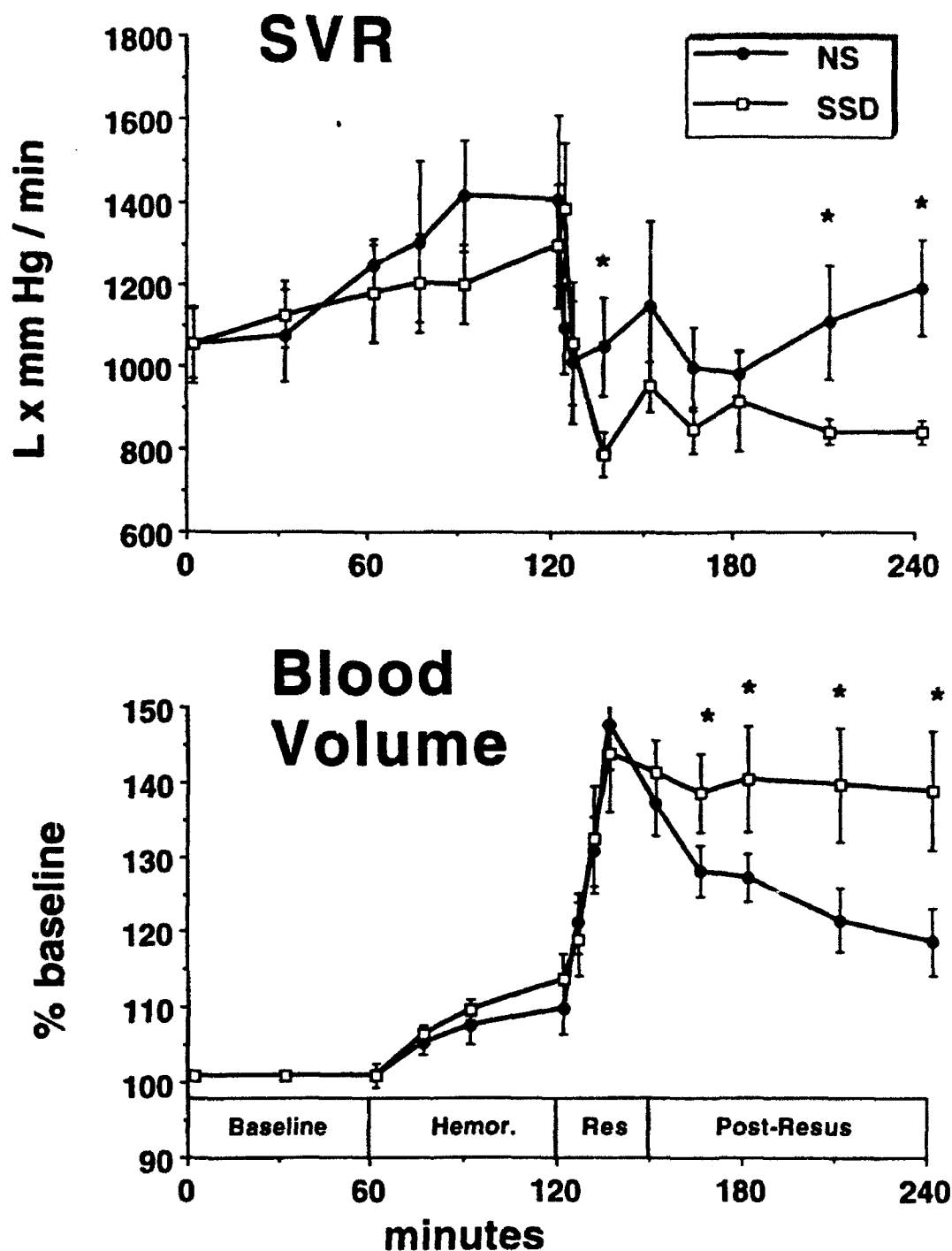


Fig 3: Systemic vascular resistance (A) and blood volume expansion (B) in hemorrhaged swine infused with NS or SSD. Data expressed as mean $\pm$ S.E. of 7 animals/group.

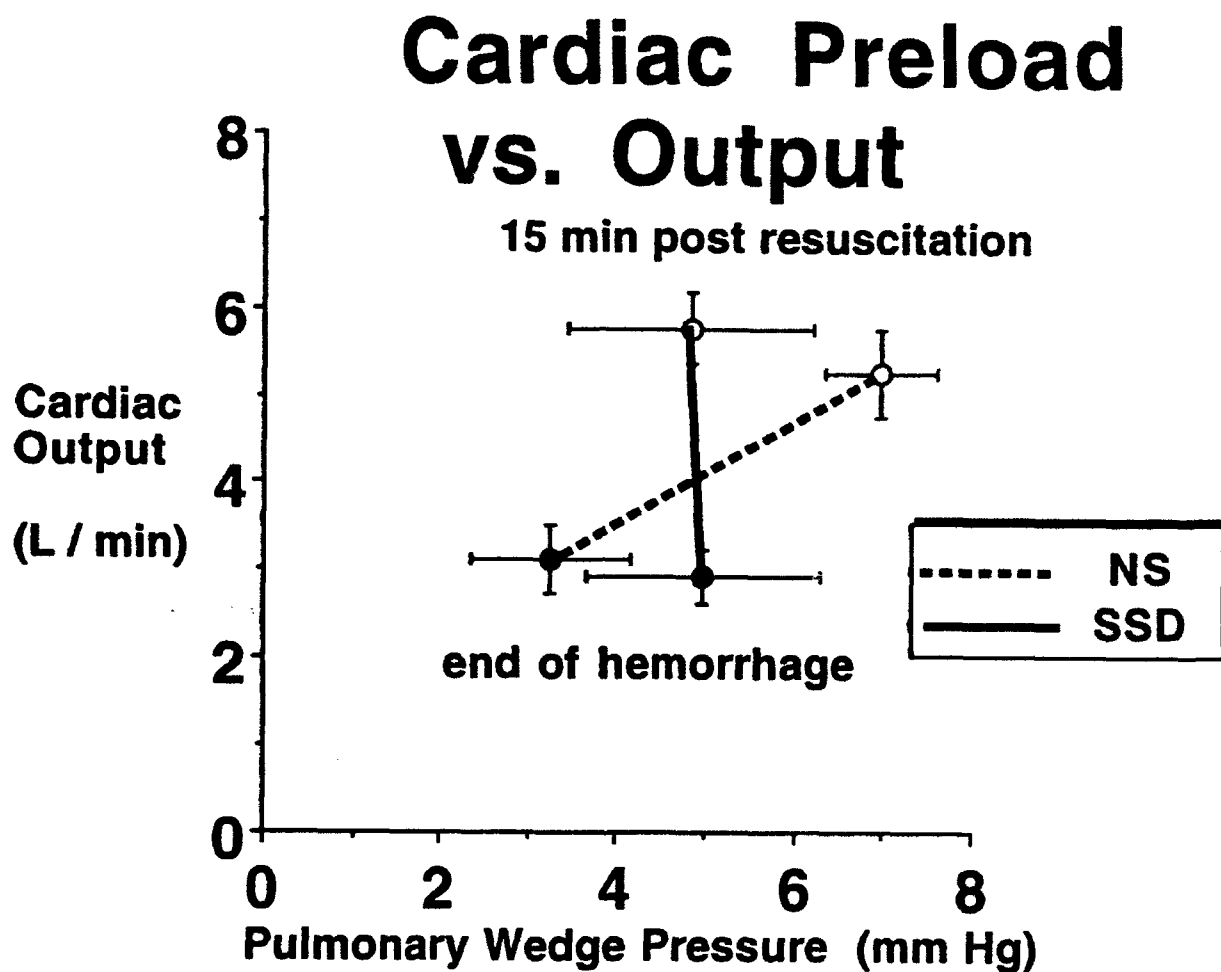


Fig 4: Cardiac preload vs. output at the end of hemorrhage and 15 min following resuscitation with NS or SSD in pigs. Data represent mean $\pm$ S.E. of 7 animals/group.

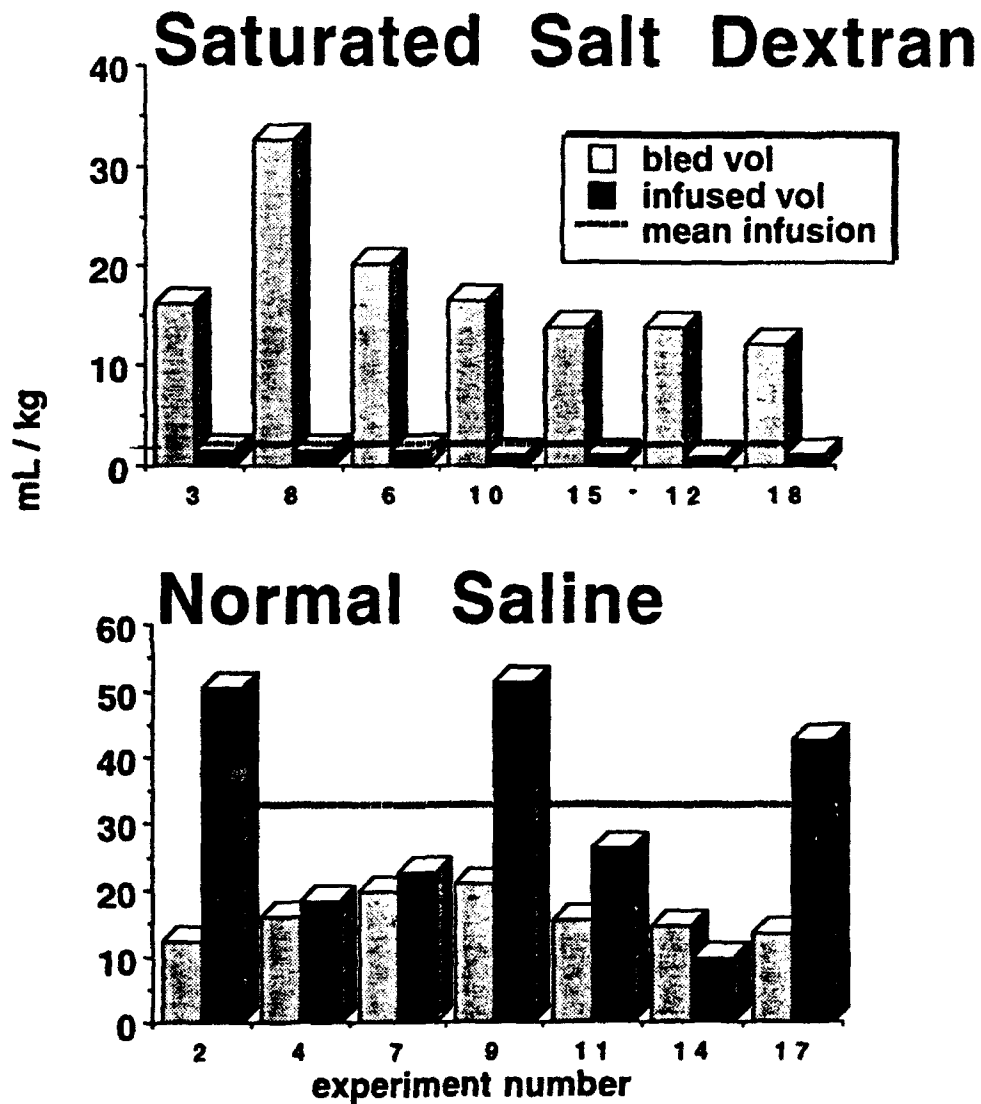


Fig 5: Comparison between volume of blood withdrawn vs. volume of SSD or NS required to achieve baseline cardiac output in hemorrhaged-resuscitated swine. Data represent 7 animals/group. Note: Data are randomly presented and are not intended to depict any particular trends.

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