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Resuscitation of Intraoperative Hypovolemia: Comparison of Normal Saline and Hyperosmotic/ Hyperoncotic Solutions in Swine

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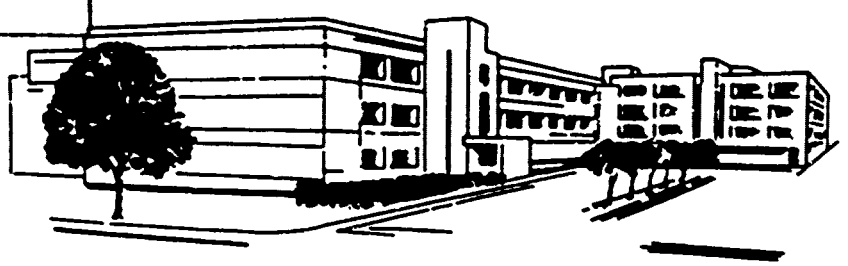

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Resuscitation of Intraoperative Hypovolemia: Comparison of Normal Saline and Hyperosmotic/Hyperoncotic Solutions in Swine, J.M. S. Pascual et al

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pressure/cardiac output relationship. We conclude that HSD resuscitation of intraoperative hypovolemia is effectively performed with smaller fluid and sodium loads, and therefore with less fluid accumulation and edema than with conventional saline solution. Furthermore, HSD resuscitation results in better cardiovascular function due to a reduction in the deleterious effects of the volume loading associated with isotonic resuscitation and possible positive inotropic effects of hypertonicity.

RESUSCITATION of INTRAOPERATIVE HYPOVOLEMIA: COMPARISON OF NORMAL SALINE AND HYPEROSMOTIC/ HYPERONCOTIC SOLUTIONS IN SWINE.

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ABSTRACT

We compared a hypertonic solution (7.5% NaCl in 6% Dextran-70, HSD) with isotonic saline (0.9% NaCl, NS) for treatment of intraoperative hypovolemia. Fourteen pigs anesthetized with isofluorane (36.3 2.1 kg) underwent a left thoracotomy, followed by hemorrhage for one hour to reduce mean arterial pressure to 45 mmHg. A continuous infusion of either solution was then initiated and the flow rate adjusted to restore and maintain thoracic descending aortic blood flow at baseline levels during a subsequent two-hour period. Full resuscitation to initial values of aortic blood flow was achieved with both regimens, but the NS group required larger volumes and sodium loads to maintain hemodynamic values. NS resuscitation produced increases in right heart preload (central venous pressure), and afterload (pulmonary artery pressure), resulting in increased right ventricular work. The HSD group had better cardiac performance as evaluated by the filling pressure/cardiac output relationship. We conclude that HSD resuscitation of intraoperative hypovolemia is effectively performed with smaller fluid and sodium loads, and therefore with less fluid accumulation and edema than with conventional saline solution. Furthermore, HSD resuscitation results in better cardiovascular function due to a reduction in the deleterious effects of the volume loading associated with isotonic resuscitation and possible positive inotropic effects of hypertonicity.

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-- Pascual et al

INTRODUCTION

Hypovolemic hypotension is a common surgical problem during extensive procedures and in patients with multiple trauma. Current resuscitative measures include infusions of blood derivatives and isotonic crystalloid solutions. Blood derivatives have limited availability and high cost, and when used in large volumes can induce such disturbances as hypocalcemia, hyperkalemia, metabolic acidosis, coagulation derangements, as well as viral infections (1). Isotonic crystalloid solutions are only effective when administered in volumes several times the vascular fluid deficit. These large doses can lead to acute hemodilution. Hemodilution reduces blood oxygen carrying capacity, thus potentially incurring hypoxic organ dysfunction. Furthermore, dilution of plasma proteins leads to a decrease in plasma colloid osmotic pressure, with the risk of subsequent interstitial fluid accumulation and edema formation (2).

Mildly hypertonic solutions have long been considered as an alternative to conventional fluid replacement (3,4), and positive results have been reported on the clinical use of 1.8% hypertonic sodium lactate solution in the management of surgical patients (5). However, an even more concentrated sodium chloride solution (7.5%) has been suggested as a rapid and effective treatment for hypovolemic shock in animals and man (6,7,8). The primary mechanism is correction of hypovolemia by rapid volume expansion due to an osmotic movement of fluid from the intracellular and interstitial spaces into the intravascular compartment (9). In addition to volume expansion, hypertonic saline infusions may augment cardiac performance by directly increasing cardiac contractility (10), reducing afterload (11), and increasing venous return through a decrease in venous capacitance (12). The inclusion of a hyperoncotic colloid such as Dextran-70 or hydroxyethyl starch to the 7.5% NaCl increases and prolongs the beneficial circulatory effects, presumably by maintaining the transferred volume within the intravascular space (13). The most striking features of resuscitation with hypertonic saline are the effectiveness of exceedingly small volumes and the rapidity of action. Moderate to severe hemorrhagic shock (bled volumes of 30-50 ml/kg) is reversed with a single intravenous injection of 4-11 ml/kg of 7.5% NaCl/6% Dextran-70 solution (HSD)

(14,15). Due to its rapid action in small volumes, HSD has been primarily proposed and used for pre-hospital resuscitation of patients with traumatic injuries. The present studies were designed to answer the following question: Is there a rationale for using hyperosmotic/hyperoncotic solutions for intraoperative treatment of hypovolemia?

Reduction in volume requirements with hypertonic resuscitation may be able to eliminate the large positive fluid balances and edema associated with conventional resuscitation regimens. Volume loading and edema may compromise cardiopulmonary hemodynamics and oxygen transport, thereby suggesting the following hypotheses: a) HSD may protect against heart failure by better normalization of conditions of preload and afterload; b) HSD improves oxygen delivery and oxygen consumption more effectively than isotonic resuscitation.

To evaluate these hypotheses we performed a moderate surgical procedure (thoracotomy) in anesthetized pigs, followed by bleeding and hypotension for one hour. The animals were then treated with either HSD or isotonic NaCl. Many of the previous studies on hypertonic resuscitation compared a 4 ml/kg infusion of HSD to an equal volume of isotonic saline (6,14). Although these studies showed HSD to be more efficient, they unfairly evaluated isotonic resuscitation which requires large volumes to be effective. A more realistic comparison of the resuscitative fluids for intraoperative use would not limit treatment to a single bolus injection. Rather, it should allow infusion until recovery to a common clinical or physiological endpoint. Accordingly, we continuously infused HSD or normal saline - 0.9% NaCl (NS), adjusting the infusion rates as needed to restore and maintain aortic blood flow and resulting cardiac output at baseline levels for a two hour period.

METHODS

ANIMAL PREPARATION: Experiments were performed on 14 immature Yorkshire pigs, wt.: 36.3 2.1 kg, randomly divided into two groups of seven animals each.

The animals were maintained on a standard diet and routinely observed for at least two weeks, and were fasted overnight before the experiment. Anesthesia was induced with ketamine HCl (2.0 mg/kg), xylazine HCl (2.0 mg/kg), atropine (0.1 mg/kg), and isoflurane 2% by mask. Following endotracheal intubation, anesthesia was maintained throughout the experiment with isoflurane (1-2%), nitrous oxide (50%) and oxygen (50%). A short-acting neuromuscular blocker (Succinylcholine 1.0 mg/kg) was administered before the beginning of the surgical manipulation. Artificial ventilation using a volume-cycled ventilator (Ohio Unitrol Ventilator, Ohio Medical Products, Madison, WI) was started using a tidal volume of 10-12 ml/kg, and adjusted throughout the experiment to maintain $_pCO_2$ within normal physiologic levels. This model was chosen based on the similarity of the responses of swine and humans to hemorrhage (16), while the anesthetic agent was selected for its ability to maintain cardiovascular stability in pigs (17).

SURGICAL PROCEDURES: After the animal was placed in a supine position, vascular catheters were inserted into the thoracic aorta via the carotid artery, into the abdominal aorta via the femoral artery, and into the inferior vena cava via the femoral vein. A balloon-tipped thermodilution catheter was positioned in the pulmonary artery via the internal jugular vein to measure pressures and cardiac output (7.5F Swan Ganz catheter). 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/min) to assure patency. Cutaneous electrodes were positioned for electrocardiographic recording. A bladder catheter was inserted by a small abdominal cutdown to obtain urine samples and to monitor urine flow rate. The animal was then laid on the right side, and a left thoracotomy was performed through the fifth intercostal space. A square wave electromagnetic flowmeter (Carolina Medical

Electronics Inc., King, NC) was positioned around the descending aorta for continuous measurement of aortic blood flow. Throughout the surgical procedure (about 2 hours) each animal received 2000 ml of warm (37°C) 0.9% saline, and was covered with an electric blanket adjusted to maintain normal body temperature.

EXPERIMENTAL PROTOCOL: Each experiment consisted of one hour of baseline observation after the completion of surgery, followed by one hour of hypovolemic hypotension and two hours of resuscitation. After the initial 60 minutes of baseline measurements, hemorrhage was induced by bleeding through the femoral artery catheter, and mean arterial pressure was reduced to 50 mmHg over a 15-minute period. For the next 45 minutes, mean arterial pressure was further reduced to 45 mmHg and maintained at that level with additional bleeding as needed. No shed blood was reinfused at any time. Then resuscitation was started by continuously infusing one of the test solutions (NS or HSD), through a peripheral vein. The initial infusion rate for both groups was calculated to deliver the same sodium load of 0.3 $mEq.kg^{-1}.min^{-1}$, i.e. flows of 2 $ml.kg^{-1}.min^{-1}$ of NS, and 0.25 $ml.kg^{-1}.min^{-1}$ for HSD. The initial rate was maintained until restoration of baseline aortic flow, then the infusion rate was reduced at 3-5 minute intervals, until establishment of the smallest flow capable of maintaining baseline aortic flow. We measured aortic blood flow using an electromagnetic flowmeter to allow on-line monitoring and prompt corrections of infusion rates. Thermodilution cardiac output measurements were performed at predetermined intervals to check the accuracy of the flowmeter. The animals were monitored for two hours; infusion rate was adjusted up or down as needed to maintain the baseline aortic flow. At the end of the experiments the animals were euthanized with a central venous infusion of saturated potassium chloride.

MEASURED VARIABLES: Hemodynamic values were measured every 20 minutes during baseline period, every 15 minutes during hemorrhage, and at 5, 10, 15, 20, 25, 30, 45, 60, 90 and 120 minutes during resuscitation. The following variables were recorded: aortic blood flow (ABF), mean systemic arterial pressure (MAP),

pulmonary artery (PAP) and pulmonary wedge (PWP) pressures, central venous pressure (CVP), cardiac output (CO), core temperature, respiratory rate, heart rate (HR) and electrocardiogram (ECG).

Arterial blood gases were measured at 15-minute intervals throughout the experiment (Instrumentation Laboratory System 1303, Instrumentation Labs, Lexington, MA), to adjust the ventilatory parameters to maintain normal levels of $_pCO_2$. Blood samples were collected as hemodynamic variables were measured during baseline and hemorrhage, and at 10, 20, 30, 45, 60, 90, and 120 minutes during resuscitation. Systemic hematocrit was determined, and levels of sodium, potassium, and total protein were analyzed in plasma, using standard laboratory methods. Twice during both baseline and hemorrhage periods, and at 10, 30, 60, and 120 minutes during resuscitation we also measured mixed venous blood gases, lactate and colloid osmotic pressure (Wescor 4100 colloid osmometer, Logan, UT). Plasma volume determinations were performed at baseline, end of hemorrhage, and at 30 and 110 minutes during resuscitation using a dye dilution (Evans blue) method (18), with injections of 2 ml (baseline and hemorrhage), 3 ml (30 minutes after the beginning of resuscitation), and 5 ml (110 minutes after the beginning of resuscitation). Samples were taken at minutes 0, 2, 4, 6 and 10 after injection. Consecutive volume measurements were corrected for the background levels of Evans blue at the time of each injection. Urinary output was recorded hourly, and samples taken for measurements of urinary sodium and potassium concentrations.

CALCULATED VARIABLES: Hemodynamic variables were calculated by means of commonly used formulas described below. All pressures were measured in mmHg, cardiac output in liters/minute and body weight (Wt.) in kg:

1) Vascular resistances (units: dynes.second.cm^{-5}):
   a) Pulmonary: (PAP-PWP)/CO x 80.
   b) Systemic : (MAP-CVP)/CO x 80.

2) Stroke work indices (units: g.meter.kg^{-1}):

a) Right ventricle: (PAPxCO)/HRx0.0136/Wt.

b) Left ventricle: (MAPxCO)/HRx0.0136/Wt.

3) Oxygen metabolism calculations (units: ml $O_2.kg^{-1}.min^{-1}$):

a) O_2 consumption: (Arterial-venous O_2 content difference) xCOx10/Wt

b) O_2 delivery: (Arterial O_2 content) xCOx10/Wt.

Other calculated variables included infused load of sodium (infused volume times sodium concentration of infusion), vascular contents of sodium, and protein (plasma concentration times plasma volume), excretion rates of sodium and potassium (urine concentration times urinary flow rate), and net fluid and electrolyte balances (infused loads minus losses due to bled volume and urinary excretion), all calculated per kg of body weight.

STATISTICS: The measured and the calculated variables were summarized for each time period by group. Student's t-test was performed to compare the groups at baseline and at end-hemorrhage periods. A two-way analysis of variance model was used with repeated measures to determine any differences between the two treatments. In addition, within each group a one-way analysis of variance was done to compare times from baseline. If a significant F was found, a Dunnett's t-test was used to determine which means differed from the baseline value. The 0.05 level of significance was used for all statistical tests.

RESULTS

HEMODYNAMICS: During baseline and hemorrhage periods there were no statistically significant differences between the groups (Table 1). Each animal was subjected to sufficient bleeding to decrease mean arterial pressure (MAP) to 45 mmHg, and to maintain this level until the beginning of resuscitation (Fig. 1). The initial infusion rate (0.3 mEq $Na.kg^{-1}.min^{-1}$)

was sufficient to restore aortic blood flow (ABF) to baseline levels in both groups, within a similar time period, and the infusion rate was adjusted thereafter according to on-line readings of ABF so that these values were maintained for two hours (Table 1). Sustained normalization of ABF was easily achieved in both groups, despite dramatic differences in infusion rates and total volume requirements for the two treatments as described below. Not only was ABF restored, but concomitant thermodilution cardiac output (CO) determinations (Fig.1) revealed a complete recovery to baseline CO levels. The arterial pressure response to resuscitation was similar in both groups, and remained below baseline values throughout the resuscitation period (Fig. 1).

Despite return to baseline values of CO and similar MAP in both groups, other hemodynamic variables were not matched. Cardiac function was significantly different between the regimens in regard to filling pressures, pulmonary hemodynamics and ventricular performances. Central venous pressure increased significantly in the NS group as compared to the HSD group (Table 1). Pulmonary wedge pressure in the NS group also exhibited a trend which was higher than in the HSD group, but this difference was not statistically significant (Table 1). These higher levels of cardiac filling pressure were not correlated with better left ventricular performance in the NS group, as equivalent levels of CO were generated under similar conditions of systemic vascular resistance (Table 1). Heart rates and left ventricular stroke work indices did not show any significant differences between treatments (Table 1 and Fig. 3, respectively). In the NS group, a large increase in mean pulmonary artery pressure of more than 13 mmHg over baseline was observed from the beginning of resuscitation; these higher levels persisted during the entire resuscitation period (Fig. 2). Likewise, pulmonary vascular resistances were significantly greater in the NS group. A consequence of these higher pulmonary pressures was an increase in the right ventricular stroke work index in the NS group compared to HSD group (Fig. 3). Our first hypothesis cannot be rejected, as HSD resuscitation was clearly associated

with an overall better normalization of cardiovascular function particularly with respect to the right ventricular preload and afterload.

BLOOD COMPOSITION: Hematocrit values fell during resuscitation (Table 2), with no significant differences between the two groups. Plasma protein also fell in both groups compared to baseline, but the fall was significantly greater in the NS group, concomitant with a similar significant decrease in the plasma colloid osmotic pressure (Table 2). Plasma lactate increased during hemorrhage, and returned to baseline values with treatment in both groups; differences between groups were not significant. Plasma sodium increased significantly with treatment in the HSD group, and remained stable at levels 12 to 14 mEq/liter higher than both baseline and the NS group (Table 2). Plasma potassium levels initially decreased in both groups during early resuscitation, but demonstrated a progressive elevation after the first 30 minutes, with no significant differences between groups (Table 2).

PLASMA VOLUMES AND VASCULAR CONTENTS: With hemorrhage, a similar loss in plasma volume was induced in both groups (Table 3). The total bleeding volume was similar, about 16.8 1.1 ml/kg and 14.6 1.8 ml/kg in the NS and HSD groups, respectively. HSD administration was accompanied by restoration of a near-baseline level of plasma volume, while in the NS group the post-resuscitation plasma volume tended to be 3-4 ml/kg higher than the initial values, not a significant difference (Table 3). Calculated total vascular content of protein after resuscitation was significantly higher in the HSD group, whereas there was no significant difference in vascular sodium contents between the groups (Table 3).

OXYGENATION VARIABLES: There were no significant differences between groups over all time points (Table 4). During early resuscitation both groups were characterized by a metabolic acidosis (Table 4) which was probably due to peripheral washout of organic acids (see lactate levels in Table 2). The HSD group showed a faster trend to normalization of pH and base

excess, while in the NS group the acidosis persisted (pH≤ 7.3 and negative values of base excess) throughout the resuscitation period, but these differences did not achieve statistical significance ($0.05 \leq p \leq 0.10$). There were no significant differences in arterial and venous pO_2 throughout the experiment. There were no significant differences in oxygen consumption index between groups throughout the experiments. The oxygen delivery index was reduced by 40-50% during hemorrhage in both groups; recovery with resuscitation was only partial compared to baseline levels, with no statistically significant difference between groups (Table 4). Thus our second hypothesis was not supported by our findings. Resuscitation with HSD did not improve oxygen delivery and consumption more than the NS regimen.

FLUID AND ELECTROLYTE BALANCE: Although an equivalent amount of blood was withdrawn from both groups, achieving full resuscitation required significantly different amounts of fluid. The NS group required an average volume of 121 22 ml/kg, while the HSD group required significantly less fluid (6.3 1.3 ml/kg), about 5% of the required NS volume. The infusion rates also presented significant differences, as after 30 minutes of resuscitation, aortic blood flow could be maintained with a drastic reduction in the HSD infusion rate to only one tenth of its initial level (Figure 4). This represents a minimal rate of 0.025 $ml.kg^{-1}.min^{-1}$ to maintain hemodynamic stability over the final 90 minutes of resuscitation.
A similar reduction was not feasible in the NS group, which required infusion rates equal to at least 50% of the initial rate for the first hour of resuscitation, and thereafter about 30-40% of initial rate to maintain aortic flow. About 80% of the total HSD requirement was infused during the first 30 minutes of resuscitation, whereas with NS only about 40% of the total volume requirement was infused by this time (Fig. 4). The urinary output was significantly decreased during hemorrhage in both groups, and was restored with resuscitation with no statistically significant differences between groups (Table 5). The total net balances revealed that the NS group had a positive

fluid balance (86.6 19.6 ml/kg) while the HSD group had a negative balance of fluid (-26.3 2.8 ml/kg.)

Besides the large difference in total volume requirements between the groups, an impressive difference in final sodium loads and balances was also apparent. The total sodium load using NS (18.7 3.3 mEq/kg) was nearly twice that of HSD (8.1 1.7 mEq/kg). Sodium excretion rate decreased during hemorrhage, and was partially restored with resuscitation, with no significant differences between groups (Table 5). Since there was no difference in the sodium excretion rates between the groups, the final net sodium balance was also higher in the NS group (16.2 4.3 mEq/kg -NS, vs. 2.5 1.5 mEq/kg -HSD). Furthermore, using mass balance we calculated the amount of sodium load lost in urine, the amount remaining in the circulation, and we were able to estimate the amount distributed to the extravascular space (Figure 5). This analysis shows that the post-resuscitation vascular sodium content in both groups was similar, and that most of the sodium load after NS treatment was extravascular, presumably interstitial. Total potassium losses in the HSD group (0.84 0.03 mEq/kg) were significantly higher than in the NS group (0.75 0.09 mEq/kg).

DISCUSSION

Clinicians have an extensive choice of fluids to correct hypovolemia, a procedure often viewed as simple volume replenishment, but perhaps more properly addressed as return of circulatory function and restoration of peripheral oxygen delivery. Optimal resuscitation would normalize vascular volume and cardiac output to meet oxygen demand, without incurring deleterious effects on the heart, lungs and peripheral organs. Blood and plasma derivatives are effective resuscitation solutions, but cost, availability and risk of infection can make them impractical. Isotonic crystalloid solutions are most commonly used, but they require infused volumes equaling 3 to 5 times the vascular deficit (2). Colloid solutions are effective in volumes equaling 1-2 times vascular losses, but in large doses colloids can induce side effects such as coagulation disorders and nephrotoxicity (19,20).

Mildly hypertonic crystalloid solutions (1.8% NaCl or Ringer's lactate solutions) have been successfully used in fluid management of surgical patients (21). They are reported to reduce total volume requirements, to reduce third space losses, and to be associated with a transient and non-detrimental increase in plasma sodium (5). Recently an interest in the clinical use of a 7.5% NaCl (2400 mOsm/l) solution has developed based on reports of its use in hypovolemic animals, as well as patients with refractory circulatory shock (6,7). Rapid improvements in blood pressure and cardiac output after a single small volume injection were reproduced experimentally by other investigators, but these improvements were found to be transient (8). However, several groups have now shown that adding a hyperoncotic colloid, Dextran-70, sustained the initial resuscitative effects of hypertonic saline (13,22,23). These studies emphasized the application of 7.5% NaCl/6% Dextran-70 (HSD) for pre-hospital resuscitation and evaluated a fixed-dose (4-6ml/kg) of both HSD and an isotonic control solution (23, 24, 25). Comparing equal and fixed doses of isotonic and hypertonic solutions can be considered an unfair comparison because isotonic fluids require large volumes to be effective. HSD and isotonic infusions have never been compared when administered as required to reach and maintain a physiologically equivalent endpoint. In the present study we resuscitated anesthetized, surgically manipulated, hypovolemic swine using continuous measurement of aortic flow to titrate infusion rate as needed for restoration and maintenance of baseline cardiac output.

We successfully normalized vascular volume and hemodynamic function using both conventional isotonic saline and a hypertonic formulation. Effective return of aortic blood flow and cardiac output were easily achieved, but arterial pressure was only partially recovered in both groups. A significant plasma volume expansion occurred in both groups with resuscitation, compared to end-hemorrhage levels. While this expansion was highly efficient in the HSD group with 2.0 ml of volume expansion per ml

infused, in the NS group there was only 0.14 ml of volume expansion per ml infused.

After 30 minutes of resuscitation, aortic blood flow could be maintained with a drastic reduction in the HSD infusion rate to a minimal rate of 0.025 $m^1.kg^{-1}.min^{-1}$, equivalent to a flow of 1.7 ml/min for a 70 kg human, compared to the equivalent required flow of 40-50 ml/min of NS in a patient of the same weight. Large volume resuscitation with NS increased venous pressures and lowered plasma colloid osmotic pressure. As reductions in colloid osmotic pressure are associated with increased microvascular filtration (26), the continuous high rate of infusion required with NS was likely due to continuous movement of fluid from the vascular compartment to extravascular spaces. These changes were in marked contrast to HSD which actually caused a net capillary reabsorption during the two hour resuscitation period.

There has been considerable concern in the literature about the sodium loads associated with HSD infusions (27). Our findings show that besides the large difference in total volume requirements between the groups, an impressive difference in final sodium loads
and balances was also apparent. The total sodium load using NS was nearly twice that of HSD, and since there was no difference in the sodium excretion rates between the groups, the final net sodium balance was also higher in the NS group, 12.5 3.6 mEq/kg for NS, vs. 2.5 1.5 mEq/kg for HSD. Furthermore, using mass balance we calculated the amount of sodium load lost in urine, the amount remaining in the circulation, and we estimated the amount distributed to the extravascular space (Figure 5). This analysis shows that the post-resuscitation vascular sodium content in both groups was similar, and that most of the sodium load after NS treatment was sequestered in the extravascular space.

With NS we observed a steady decay in plasma protein levels, probably related to acute hemodilution and associated with a highly significant reduction in colloid osmotic pressure to levels 50% lower than

baseline. This was not observed in the HSD group, where both plasma protein and colloid osmotic pressure remained at levels only slightly lower than baseline. Dextran is partly responsible for the maintenance of the colloid osmotic pressure, but the vascular content of protein was also significantly greater in the HSD group, thereby suggesting two possibilities: 1) large volume NS resuscitation may increase capillary filtration and connectively move protein out of the vascular space (26); 2) HSD treatment may stimulate lymphatic pumping and augment vascular return of protein. These microcirculatory events could contribute to the remarkable efficiency of HSD resuscitation.

Several physiological differences of potential clinical significance between hypertonic and isotonic resuscitation were noted in pulmonary hemodynamics and cardiac performance. Our most striking finding was a large acute increase in central venous pressure, pulmonary artery pressure (PAP) and pulmonary vascular resistances during NS resuscitation. A consequence of the high PAP was the sustained increase in right ventricular stroke work index. The large volume resuscitation and the concomitant dilution of plasma protein may have induced an increase in extravascular lung water. This event may be correlated with the transient fall in arterial pO_2 observed during early resuscitation in the NS group, by interfering with oxygen diffusion through the alveolar wall. Likewise, increased interstitial lung volume may decrease effective vascular compliance and increase resistance to blood flow, thereby causing an increase in pulmonary pressures and right ventricular work. HSD treatment restored baseline levels of both pulmonary pressures and vascular resistances. Hypertonic resuscitation causes a net decrease in extravascular fluid which may keep lung vascular compliance high and vascular resistance low (28). Additionally, hyperosmolarity is known to have direct vasodilator effects on pulmonary vessels (29,30).

Increases in heart rate and contractility after hypertonic infusions have been previously reported and attributed to increased adrenergic activity (10,31).

However, other studies showed that adrenergic beta-blockade suppressed only the chronotropic response and not the increased contractility after hyperosmotic infusions, thus suggesting a direct positive inotropic effect (32,33). Isolated myocardial cells exposed to hyperosmolar media exhibit an increased intracellular free calcium, thereby offering an explanation for the positive inotropic effect (34).

The analysis of the main determinants of cardiac performance in our experiments indeed suggests a difference in inotropic state between groups. During resuscitation preload conditions were significantly higher in the NS group, as evaluated by central venous pressure. Arterial pressure and afterload were similar in both groups; both groups had an equivalent decay in peripheral resistance during resuscitation which was probably primarily induced by volume restoration. It has been suggested that HSD-induced vasodilatation is more evident when HSD is administered with a fast injection, and we conjectured that a slow, continuous infusion might attenuate that effect (35). There was no significant difference between the heart rates of the groups. Thus, in view of similar conditions of afterload and heart rate, one should expect that the better preload conditions in the NS group would be correlated with better cardiac performance. We did not directly measure myocardial contractility, but the plotting of pulmonary wedge pressures vs. cardiac output before and 10 minutes after resuscitation (Fig. 6), suggests a difference in the Starling cardiac function curves. These data are consistent with a higher inotropic state in the HSD group, or a contractile depression after NS treatment, perhaps associated with an increase in the heart's interstitial water. These observations may be relevant to management of patients with a previous history of right ventricular or congestive heart failure. HSD may be advantageous in these patients as it induces a better pulmonary hemodynamic profile and an improved cardiac function.

Previous investigators of HSD have emphasized its effectiveness and speed in small volumes, and its potential in pre-hospital environments where adequate

volumes of conventional fluids are difficult to administer (12,25). The present study evaluated the potential of HSD for intraoperative use. Using both HSD and NS we have demonstrated successful normalization of systemic blood flow after anesthesia, surgery and hypovolemia. Our results suggest that HSD offers several physiological and clinical benefits and may prevent some of the deleterious effects induced by conventional large volume resuscitation. HSD was associated with smaller total loads of fluids and sodium, and with better cardiac performance. The increase in pulmonary pressures in the NS group can be considered a potentially dangerous burden to the right ventricle, especially under conditions of decreased oxygen transport and metabolic acidosis. HSD may be less likely to induce cardiovascular overload and peripheral edema, and may protect against pulmonary edema and right heart failure. The clinical applications of HSD may not be limited to pre-hospital use, but may be extended to the surgical environment, perhaps not only to treat hemorrhagic shock, but whenever efficient and effective volume replacement and circulatory support are needed.

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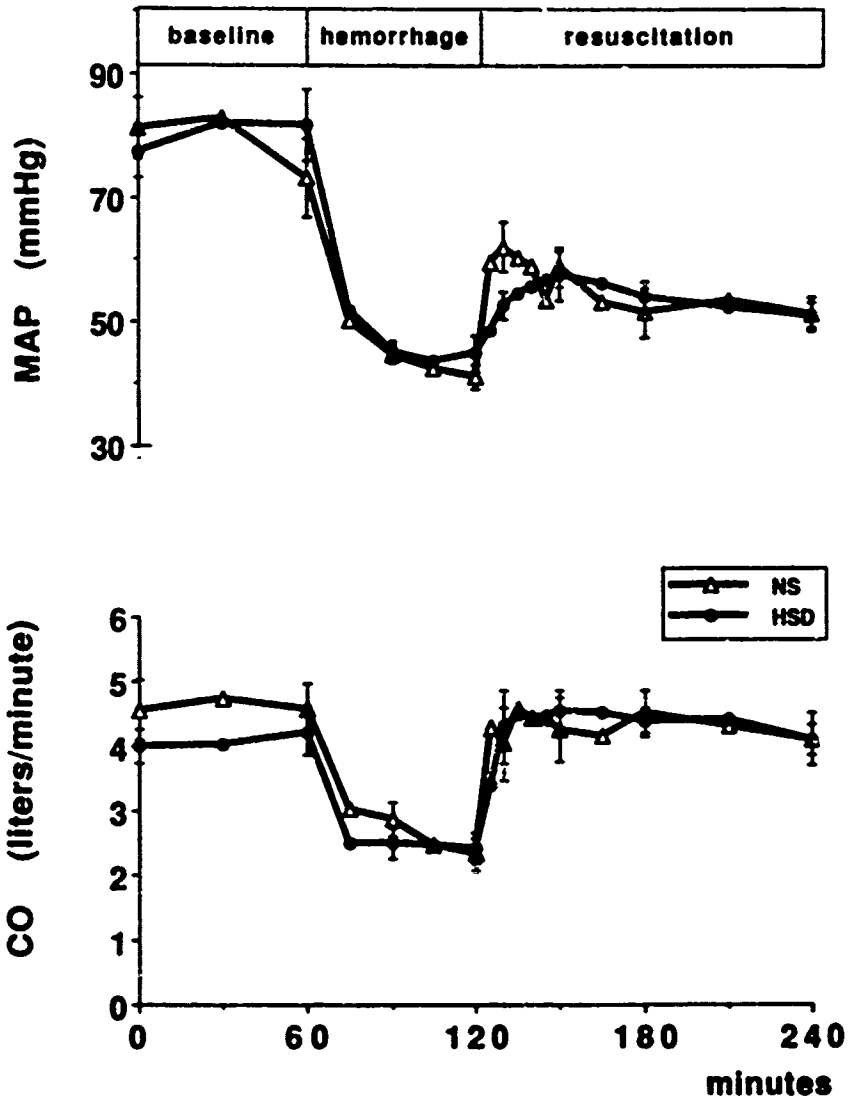

Figure 1. Mean arterial pressure (MAP) and cardiac output (CO) during baseline, hemorrhagic hypotension, and resuscitation periods with 0.9% NaCl (NS), and 7.5% NaCl/6% Dextran-70 (HSD). Values are the mean SEM for 7 animals in each group. There were no statistically significant differences between the MAP and CO of the two groups.

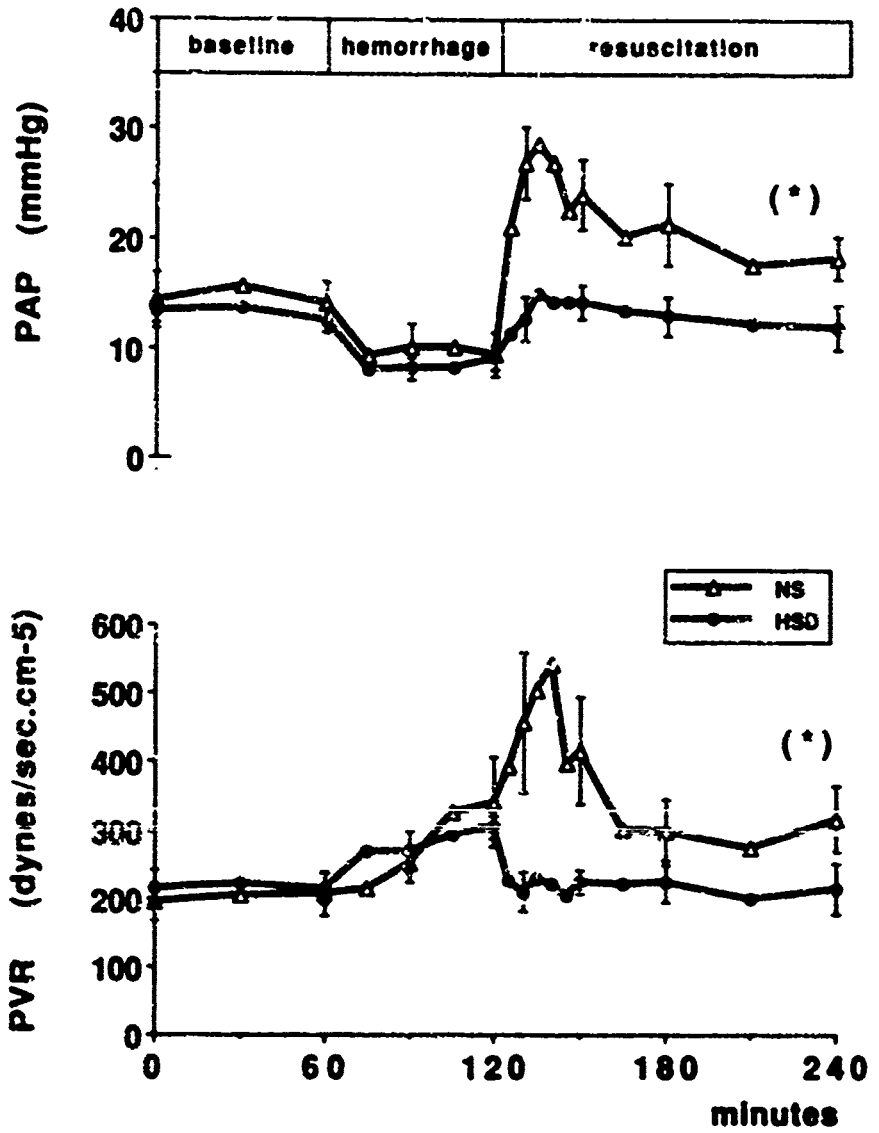

Figure 2. Mean pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) of the same groups and time points as Fig. 1. (*) = significant difference ($p < 0.05$) NS vs. HSD over all time points following resuscitation.

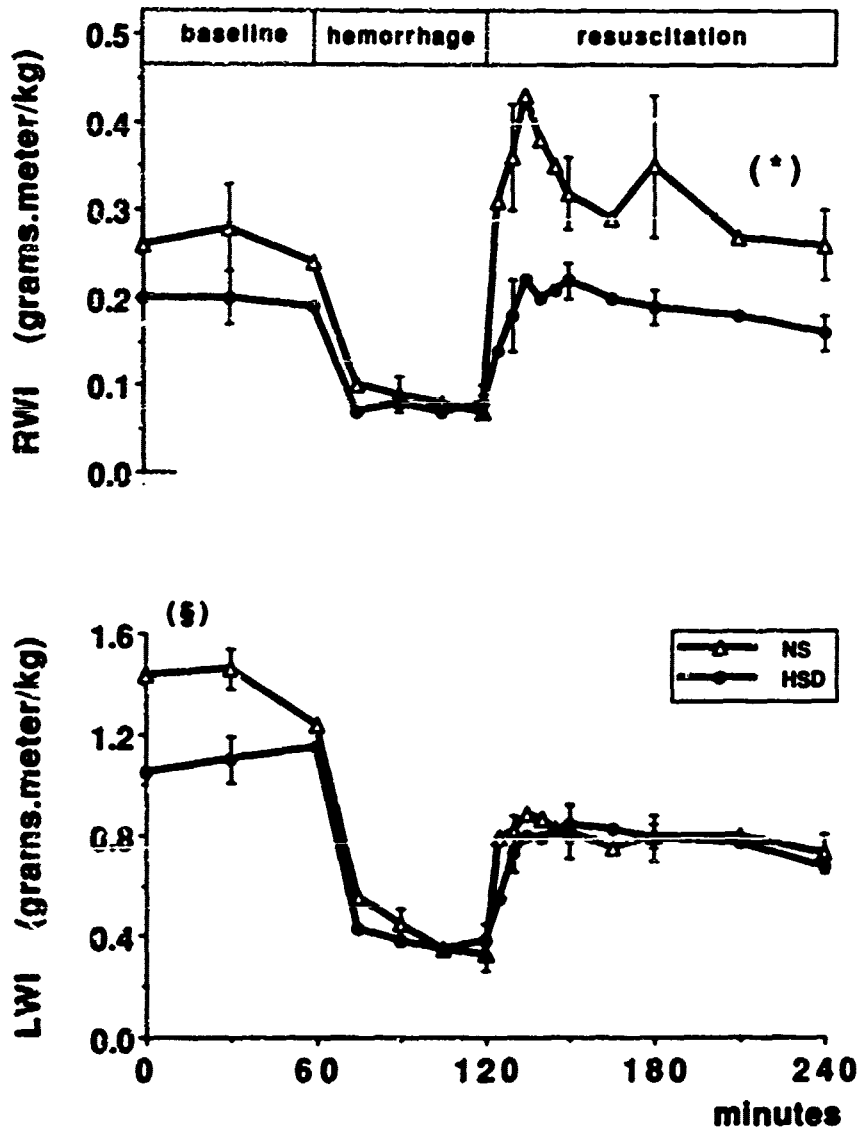

Figure 3. Right (RWI) and left (LWI) ventricular stroke work indices, calculated at the same time points and groups of Fig. 1. (*)= significant difference ($p < 0.05$) NS vs. HSD over all time points following resuscitation. (§)=significant difference ($p < 0.05$) NS vs. HSD during baseline, but not during hemorrhage and resuscitation.

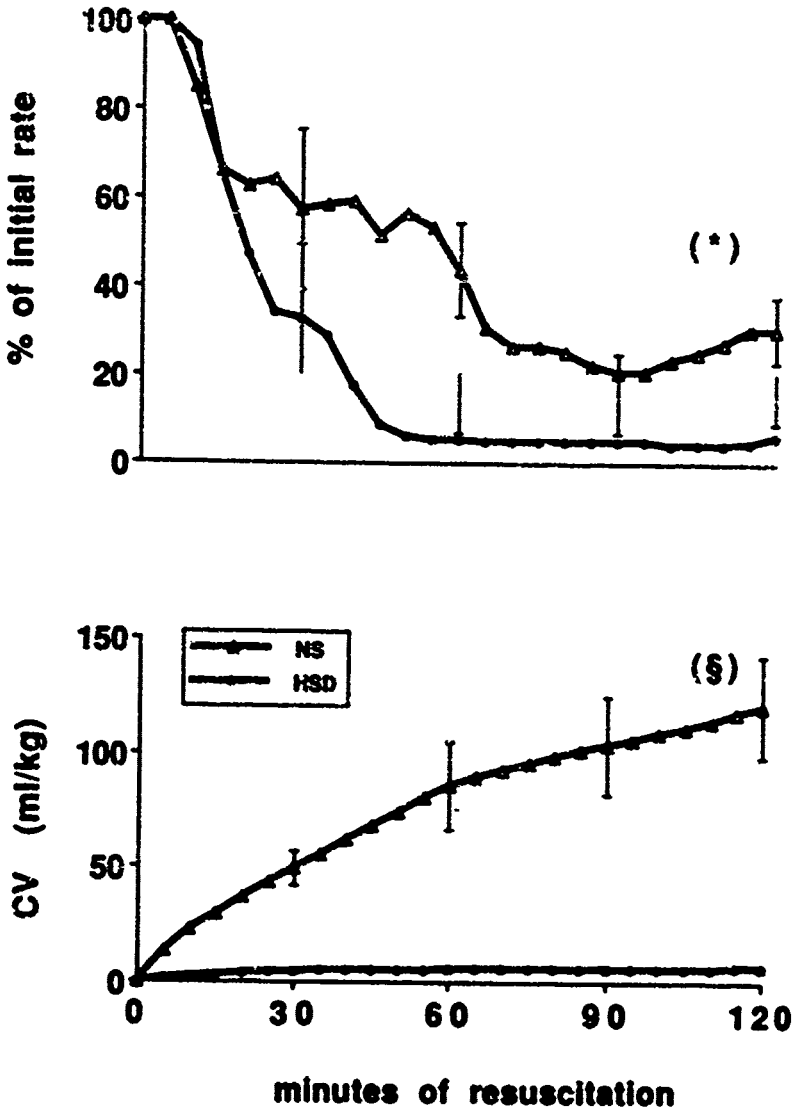

Figure 4. Changes in infusion rates expressed as percentage of initial rate of 0.9% NaCl (NS), and 7.5% NaCl/6% Dextran-70 (HSD) and total cumulative infused volumes (CV), in the same two groups. (*) = significant difference ($p < 0.05$) NS vs. HSD over all time points after 30 minutes of resuscitation. (§) = significant difference ($p < 0.05$) NS vs. HSD over all time points.

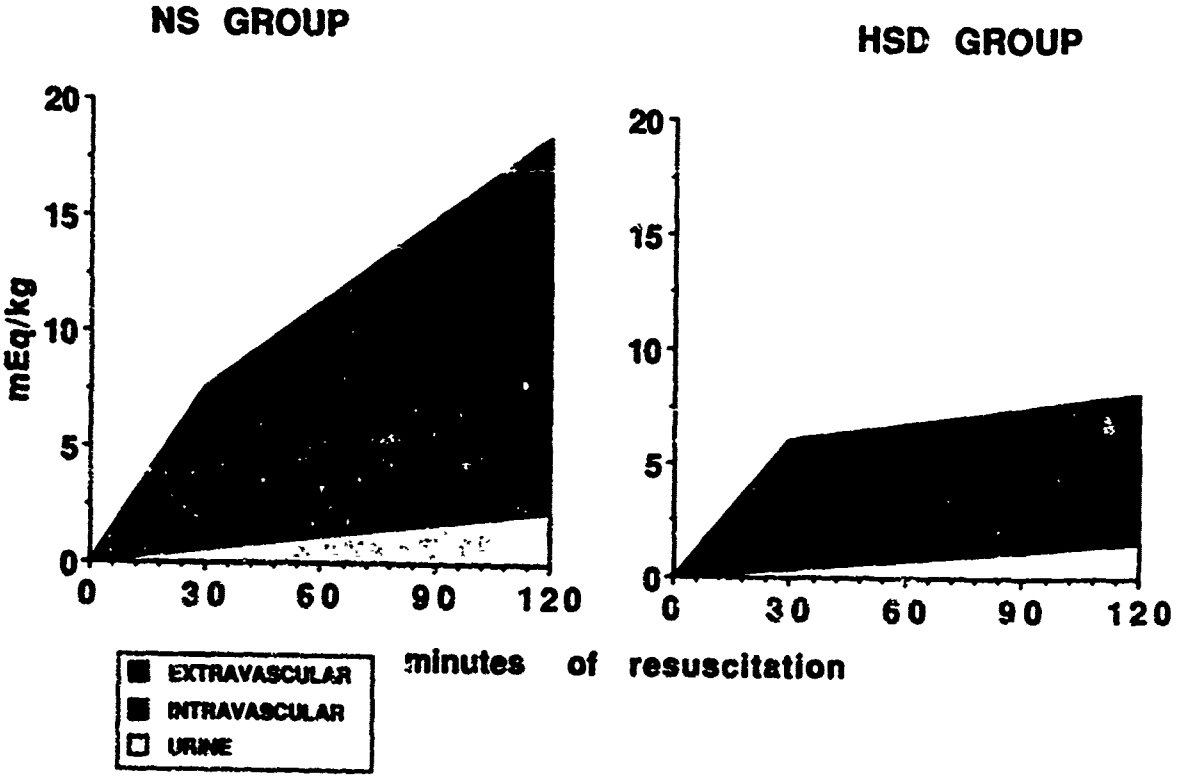

Fig. 5. Estimated distribution of the infused sodium load of NS and HSD treatment. Extravascular and intravascular sodium contents, and urinary sodium excretion were calculated by mass balance throughout the resuscitation period.

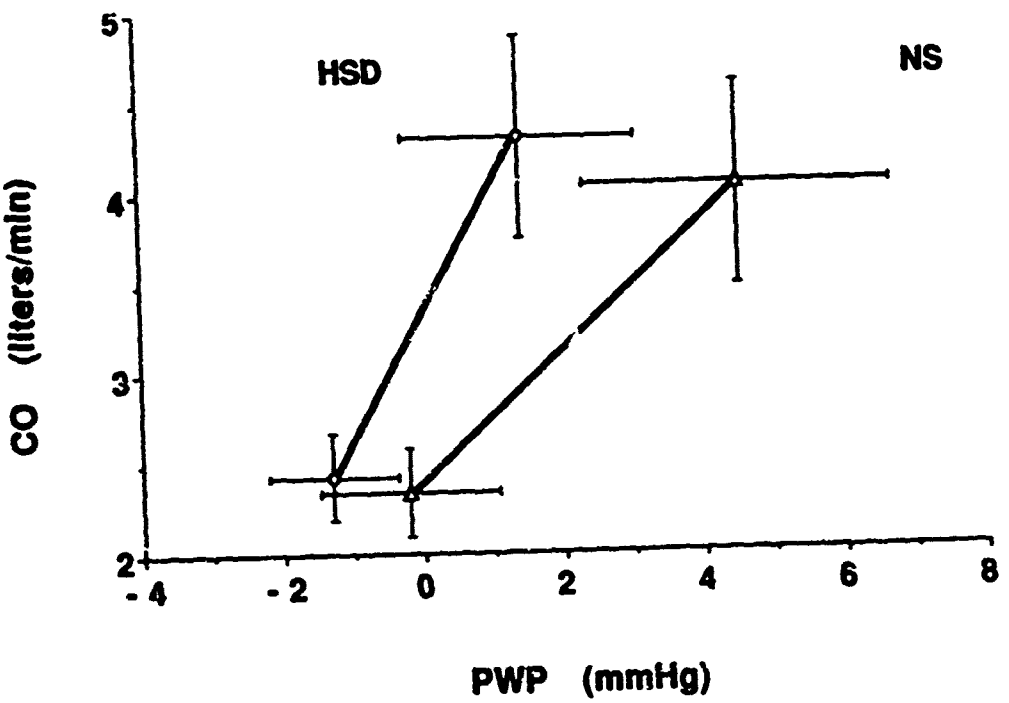

Figure 6. Left ventricular filling pressure (pulmonary wedge pressure - PWP) vs. cardiac output (CO) at end-hemorrhage period (hollow symbols) and after 10 minutes of resuscitation (full symbols), in the same groups described in Fig. 1. The more accentuated slope in the HSD group suggests a higher inotropic state. Values are mean SEM, n= 7 animals per group.

TABLE 1 - HEMODYNAMIC VARIABLES

		BASELINE	30' HEM	60' HEM	5' RES	10' RES	30' RES	60' RES	120' RES	
AORTIC BLOOD FLOW										
(liters/min)	NS	2.9±0.5	1.5±0.3	1.0±0.2	2.1±0.5	2.4±0.4	2.8±0.4	2.6±0.4	2.6±0.3	
	HSD	2.4±0.4	1.2±0.2	1.2±0.3	1.8±0.3	2.3±0.4	2.9±0.4	2.7±0.3	2.5±0.3	
CENTRAL VENOUS PRESSURE										
(mmHg)	NS	0.3±0.9	-1.6±1.0	-1.9±1.3	2.1±1.1	2.6±0.9	3.5±1.4	3.8±1.8	3.5±1.4	(*)
	HSD	-0.8±0.9	-3.1±1.0	-4.3±1.2	-2.6±1.1	-2.1±1.1	-2.1±1.2	-2.6±1.2	-2.9±1.3	
PULMONARY WEDGE PRESSURE										
(mmHg)	NS	2.7±0.9	0.3±1.6	-0.2±1.3	2.2±1.5	4.5±2.2	4.2±0.7	4.3±1.4	2.8±0.8	
	HSD	2.6±0.9	-0.1±0.9	-1.3±0.9	1.2±1.7	1.4±1.7	1.0±1.1	0.3±1.3	0.5±1.3	
HEART RATE										
(beats/min)	NS	105±4	127±15	143±24	125±15	122±12	127±13	119±14	121±14	
	HSD	110±10	107±11	116±13	115±13	113±11	112±10	113±10	112±11	
SYSTEMIC VASCULAR RESISTANCE										
(dynes.sec/cm5)	NS	1564±260	1374±147	1548±159	1276±171	1271±138	1107±110	875±116	993±127	
	HSD	1730±253	1668±215	1612±162	1280±169	1109±127	1086±117	1054±85	1081±84	

(*) = significant difference ($p < 0.05$) NS vs. HSD over all time points following resuscitation.

TABLE 2 - BLOOD COMPOSITION ANALYSES

		BASELINE	30' HEM	60' HEM	10' RES	30' RES	60' RES	120' RES	
HEMATOCRIT									
(%)	NS	28.4 ± 0.9	27.3 ± 0.8	27.1 ± 1.2	20.0 ± 0.7	20.7 ± 0.8	19.1 ± 0.5	19.5 ± 0.8	
	HSD	28.4 ± 1.2	27.2 ± 1.1	27.0 ± 1.4	21.5 ± 0.9	19.0 ± 0.7	18.5 ± 1.0	19.1 ± 1.0	
TOTAL PROTEIN									
(grams/dl)	NS	5.1 ± 0.2	4.8 ± 0.3	4.6 ± 0.2	3.5 ± 0.3	3.2 ± 0.2	3.1 ± 0.3	3.2 ± 0.3	(*)
	HSD	5.5 ± 0.3	5.0 ± 0.3	4.8 ± 0.3	4.2 ± 0.2	4.2 ± 0.2	4.3 ± 0.1	4.3 ± 0.1	
COLLOID OSMOTIC PRESSURE									
(mmHg)	NS	12.3 ± 0.6	11.2 ± 0.6	10.4 ± 0.5	8.0 ± 0.6	7.1 ± 0.6	6.4 ± 0.7	4.2 ± 0.6	(*)
	HSD	12.7 ± 0.6	12.0 ± 0.5	11.2 ± 0.7	10.6 ± 0.7	10.5 ± 0.5	10.6 ± 0.4	10.4 ± 0.5	
LACTATE									
(mg/dl)	NS	16.2 ± 2.7	20.7 ± 2.8	26.3 ± 3.6	25.8 ± 4.0	26.2 ± 3.4	21.8 ± 2.8	18.4 ± 2.7	
	HSD	9.9 ± 1.8	11.6 ± 1.8	17.2 ± 2.9	20.1 ± 4.7	19.8 ± 5.5	16.6 ± 4.5	13.7 ± 3.8	
SODIUM									
(mEq/liter)	NS	140 ± 0.6	140 ± 0.5	140 ± 0.7	142 ± 0.8	143 ± 0.6	143 ± 0.6	144 ± 0.6	(*)
	HSD	142 ± 0.7	142 ± 0.8	141 ± 0.7	156 ± 1.0	156 ± 2.8	154 ± 2.1	154 ± 2.1	
POTASSIUM									
(mEq/liter)	NS	4.4 ± 0.1	4.8 ± 0.2	4.7 ± 0.2	3.9 ± 0.3	3.8 ± 0.1	3.8 ± 0.3	4.4 ± 0.3	
	HSD	4.5 ± 0.1	4.7 ± 0.1	4.7 ± 0.1	3.9 ± 0.1	4.0 ± 0.1	4.4 ± 0.2	4.9 ± 0.2	

(*) = significant difference ($p < 0.05$) NS vs. HSD over all time points following resuscitation.

TABLE 3 - PLASMA VOLUME AND VASCULAR CONTENTS

		BASELINE	HEM	30' RES	60' RES	
PLASMA VOLUME						
(ml/kg)	NS	52.3 ± 3.6	38.7 ± 2.9	56.1 ± 3.9	56.4 ± 3.4	
	HSD	52.9 ± 4.7	36.7 ± 2.0	50.4 ± 3.2	50.4 ± 4.4	
VASCULAR PROTEIN		(§)				
(grams/kg)	NS	2.7 ± 0.2	1.8 ± 0.9	1.8 ± 0.2	1.8 ± 0.2	(*)
	HSD	3.1 ± 0.4	1.8 ± 0.2	2.2 ± 0.2	2.2 ± 0.2	
VASCULAR SODIUM						
(mEq/kg)	NS	7.1 ± 0.7	5.3 ± 0.6	8.0 ± 0.8	8.3 ± 0.6	
	HSD	7.5 ± 0.7	5.2 ± 0.3	7.8 ± 0.5	7.7 ± 0.7	

(§) = significant difference ($p < 0.05$) NS vs. HSD at baseline, but not at hemorrhage

(*) = significant difference ($p < 0.05$) NS vs. HSD over all time points following resuscitation.

TABLE 4 - BLOOD GASES DATA

		BASELINE	HEMORRHAGE	10' RES	30' RES	60' RES	120' RES
pH	NS	7.40 ± 0.01	7.38 ± 0.01	7.32 ± 0.04	7.28 ± 0.03	7.27 ± 0.03	7.30 ± 0.03
	HSD	7.43 ± 0.02	7.41 ± 0.01	7.34 ± 0.02	7.35 ± 0.01	7.36 ± 0.01	7.35 ± 0.02
BASE EXCESS (mEq/liter)	NS	0.8 ± 0.6	-1.8 ± 1.0	-4.2 ± 1.3	-5.1 ± 1.7	-5.9 ± 1.5	-5.8 ± 1.3
	HSD	1.0 ± 0.4	-0.4 ± 0.6	-2.5 ± 0.6	-2.5 ± 0.8	-1.6 ± 1.0	-2.2 ± 1.4
ARTERIAL pO2 (mmHg)	NS	244 ± 14	256 ± 21	203 ± 33	245 ± 13	227 ± 18	207 ± 23
	HSD	204 ± 11	232 ± 8	225 ± 11	226 ± 8	199 ± 18	201 ± 16
VENOUS pO2 (mmHg)	NS	52 ± 3	33 ± 2	43 ± 3	49 ± 4	45 ± 3	45 ± 5
	HSD	46 ± 2	37 ± 3	43 ± 2	44 ± 2	42 ± 3	39 ± 4
O2 CONSUMPTION (ml O2/min/kg)	NS	3.5 ± 0.4	3.9 ± 0.5	3.7 ± 0.5	3.9 ± 0.6	4.3 ± 0.7	3.6 ± 0.6
	HSD	3.0 ± 0.3	2.9 ± 0.5	3.6 ± 0.4	3.6 ± 0.5	3.3 ± 0.4	3.7 ± 0.6
O2 DELIVERY (ml O2/min/kg)	NS	17.8 ± 0.71	9.0 ± 0.90	11.4 ± 1.41	12.7 ± 1.30	12.3 ± 0.67	11.3 ± 0.96
	HSD	14.2 ± 1.02	8.1 ± 0.85	11.4 ± 1.28	11.1 ± 1.05	10.2 ± 0.68	9.8 ± 0.77

no significant differences ($p > 0.05$) between groups over all time points following resuscitation.

TABLE 5 - FLUID AND ELECTROLYTE EXCRETION DATA

		BASELINE	HEMORRHAGE	60' RES	120' RES
URINARY OUTPUT					
(ml/kg/hour)	NS	5.1 ± 0.9	1.1 ± 0.4	5.6 ± 1.5	5.4 ± 2.6
	HSD	9.0 ± 1.7	1.4 ± 0.3	3.9 ± 0.8	3.7 ± 0.7
Na EXCRETION					
(mEq/kg/hour)	NS	1.1 ± 0.2	0.2 ± 0.1	1.2 ± 0.2	1.1 ± 0.4
	HSD	1.6 ± 0.3	0.2 ± 0.0	0.8 ± 0.2	0.8 ± 0.2
K EXCRETION					
(mEq/kg/hour)	NS	0.32 ± 0.03	0.08 ± 0.02	0.19 ± 0.03	0.17 ± 0.03
	HSD	0.34 ± 0.04	0.07 ± 0.01	0.18 ± 0.02	0.24 ± 0.03

no significant differences ($p > 0.05$) between groups over all time points following resuscitation.

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