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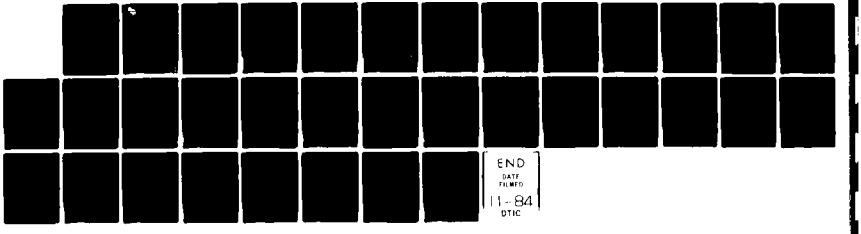

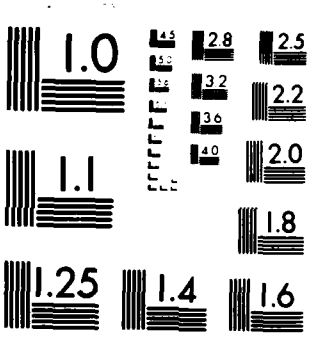

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FATAL HEMORRHAGIC SHOCK AND ACETATE SOLUTIONS

L. WILLIAM TRAVERSO, MD, MAJ(P) MC
WYNE P. LEE, BVS, SP4
MICHAEL J. LANGFORD, DVM, CPT(P) MSC
and
L. DENISE WITCHER, BS, SP5

DIVISION OF COMBAT CASUALTY CARE

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PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129

Fatal Hemorrhagic Shock and Acetate Solutions--Traverso, Lee, Langford, and Witcher

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20. ABSTRACT

One-half of deaths among trauma victims occur within 1 hours of injury and are due to rapid hemorrhage or CNS trauma. We developed a rapid hemorrhage model in unanesthetized swine to simulate human exsanguination. We compared the ability of four crystalloid solutions to prevent death after an otherwise fatal hemorrhage; normal saline (NS), Ringer's lactate (RL), Plasmalyte-A (PA), and Plasmalyte-R (PR). Five days before hemorrhage swine received an aortic sideport and a central venous treatment catheter. Aortic blood (54ml/kg) was removed in 15 minutes from 116 swine. The percentage of shed blood replaced was 14 percent in 5 minutes with NS, 100 percent in 20 minutes with NS, and 300 percent in 30 minutes with NS, RL, PA, or PR. We found that all mortalities were determined within two hours after hemorrhage and that RL provided the best survival rate of 67 percent (NS 300%=50%, PR=40%, and PA=30%). After an analysis of arterial blood gas, lactate, acid-base, heart rate, and aortic pressure measurements, we conclude that RL is the superior crystalloid solution because of its decreased chloride load (as compared to NS) and because of the absence of acetate or magnesium (as compared to PA and PR).

ABSTRACT

One-half of deaths among trauma victims occur within 1 hour of injury and are due to rapid hemorrhage or CNS trauma. We developed a rapid hemorrhage model in unanesthetized swine to simulate human exsanguination. We compared the ability of four crystalloid solutions to prevent death after an otherwise fatal hemorrhage: normal saline (NS), Ringer's lactate (RL), Plasmalyte-A (PA), and Plasmalyte-R (PR). Five days before hemorrhage swine received an aortic sideport and a central venous treatment catheter. Aortic blood (54 ml/kg) was removed in 15 minutes from 116 swine. The percentage of shed blood replaced was 14 percent in 5 minutes with NS, 100 percent in 20 minutes with NS, and 300 percent in 30 minutes with NS, RL, PA, or PR. We found that all mortalities were determined within two hours after hemorrhage and that RL provided the best survival rate of 67 percent (NS 300%=50%, PR=40% and PA=30%). After an analysis of arterial blood gas, lactate, acid-base, heart rate, and aortic pressure measurements, we conclude that RL is the superior crystalloid solution because of its decreased chloride load (as compared to NS) and because of the absence of acetate or magnesium (as compared to PA and PR).

PREFACE

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FATAL HEMORRHAGIC SHOCK AND ACETATE SOLUTIONS

Hemorrhagic shock following rapid exsanguination occurs frequently in civilian and combat injuries. According to Trunkey (1), one-half of civilian trauma deaths occur from exsanguination or central nervous system trauma within an hour of injury. Within 2 to 3 hours after injury 30 percent more civilian trauma deaths occur. These are due to major internal hemorrhage (1). According to the Department of Defense (2), of the 43,601 combat deaths due to hostile forces between 1 January 1961 and 31 December 1975 during the Vietnam War, 88 percent were killed in action. Bellamy (3) calculated that one-half of the soldiers killed in action died of rapid hemorrhage. About 12 percent of the total combat-related deaths (5168) occurred after hospitalization in Vietnam (2). Arnold and Cutting (4) found head injury to be the most common cause of these hospital deaths (42%) followed by hemorrhagic shock (24%). Since rapid hemorrhage is prevalent in civilian trauma and combat casualties, it is important to determine the best form of treatment other than blood. Hemorrhage control is the sine qua non of effective treatment but, after hemorrhage is controlled, what blood replacement solution is the agent of choice?

This study was designed to survey conventional crystalloid resuscitation methods in the treatment of otherwise fatal exsanguination. We developed a porcine fixed-volume hemorrhage model to mimic the rapid exsanguination shock victim (5). This unanesthetized and unheparinized model is 100 percent fatal if untreated, and yet, 90 percent of the animals survive if all of their blood is returned in 30 minutes (6). The hemorrhage model of this study does not completely reproduce the actual injury of the combat casualty or civilian victim because the added insult of tissue trauma is absent; thus the rigidly controlled hypovolemic condition is the isolated independent variable. However, even in the absence of direct tissue injury, the hemorrhage-to-death interval of this experimental model is similar to the interval observed after human trauma.

First we calibrated the model's response to increasing shed blood replacement with normal saline. Then we compared a 300 percent replacement of shed blood with four crystalloid solutions. We found that Ringer's lactate was associated with the best survival rate because of its decreased chloride concentration (as compared to normal saline) and the absence of acetate or magnesium (as compared to Plasmalyte-A and Plasmalyte-R).

MATERIALS AND METHODS

Surgical Placement of Hemorrhage and Treatment Catheters.

Immature female swine between 32 and 53 lb (15-24 kg) were anesthetized with endotracheal halothane 5 days before hemorrhage. All surgical procedures were done by the same investigator (LWT). Under sterile conditions and by left retroperitoneal dissection, a polyvinylchloride catheter (OD=3.7 mm, ID=2.6 mm) was placed as a sideport in the infrarenal aorta and anchored to the vessel wall with suture via a polyester patch cemented to the catheter (Figure 1). The aortic end of the catheter previously was cut to be flush with the inner aortic wall. The catheter was tunnelled from the retroperitoneum medial to the paraspinal muscles where it exited the skin in the midline lumbar area, then it was anchored to the skin with nylon suture. The area was covered with a double Velcro patch which was also sutured to the skin. The aortic sideport has increased the incidence of successful exsanguination in unheparinized swine from 81 percent to 95 percent in our last 229 preparations (7). Details of catheter construction and operative placement have been described previously (7). An intravenous treatment catheter of polyvinylchloride (OD-2.8 mm, ID-1.8 mm) was threaded into a supra-atrial position through the left external jugular vein through a neck incision. The catheter was tunneled to exit the skin in the midline dorsal cervical area, sutured to the skin, and also protected with a Velcro patch. At the end of the surgical procedure, both catheters were filled with 2 ml of sterile unheparinized 0.9 percent NaCl, containing 40 mg of gentamicin. The catheters were not disturbed again until the day of hemorrhage.

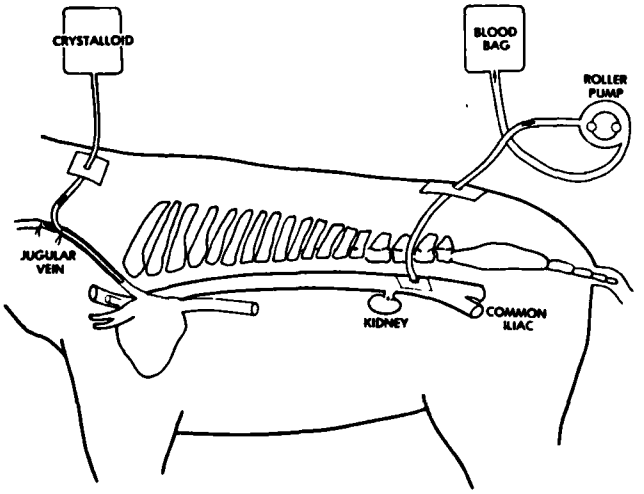

Figure 1. **The distal aortic sideport catheter and central venous treatment catheter used in this study of an unheparinized and unanesthetized hemorrhage model in swine.**

Hemorrhage and Treatment Methods

All swine (n=116) had 54 ml/kg of blood removed in 15±2 minutes as previously described (5). The hemorrhage catheter was attached to a roller pump (Model #610, Bio-Rad Laboratories, Richmond, CA) with silicone rubber tubing (OD=5.0 mm, ID=1.75 mm). The rate of hemorrhage was adjusted by measuring the weight of blood collection bags or the accumulating volume of pump effluent in a graduated cylinder. Within 4 minutes after the end of hemorrhage, a treatment regimen was begun through the intravenous catheter. The prehemorrhage weight, hemorrhage time, treatment type, and treatment time of the swine were recorded. Survival of the animal was then observed with death defined as apnea and unresponsiveness to stimuli. A survivor was defined as a swine that lived for 24 hours.

Treatment Groups

Table 1 lists the treatment type, percentage of shed blood replaced, and times over which the treatments were administered. The increasing volume replacements with normal saline were designed to administer the fluid at an increasing rate up to 6 ml/kg/min. Treatments were chosen at random on a daily basis over a 10-month period except for the PR group which was carried out over a 1-month period. The average pH, osmolarity, and electrolyte concentration of each solution is shown in Table 2.

TABLE 1

Treatment Group Outline

Fluid Treatment	Abbreviation in Text	n	Shed Blood Replaced (%)	Treatment Time (min)	No. of Survivors Autopsied
Normal Saline	NS 14%	15	14	4±1	0
Normal Saline	NS 100%	20	100	20±2*	1
Normal Saline	NS 300%	20	300	30±3	3
Ringer's Lactate	RL	21	300	30±3	1
Plasmalyte-A	PA	20	300	30±3	2
Plasmalyte-R	PR	20	300	30±3	1

*During 100% replacement if treatment time was prolonged to 30 min, many animals would die during treatment.

TABLE 2

Specification of Crystalloid Solutions

Solution*	pH	mOsm/l	Na	K	Cl	Ca	Mg	HCO_3 (Source)
			<----------(mEq/liter)------>					
Normal Saline	5.0	308	154		154			
Ringer's Lactate	6.5	272	130	4	109	3		28 (Lactate)
Plasmalyte-A	7.4	288	140	5	98	0	3	27 (Acetate) 23 (Gluconate)
Plasmalyte-R	5.5	312	140	10	103	5	3	47 (Acetate) 8 (Lactate)

* = manufacturer's published values

All solutions were obtained commercially (Travenol Labs, Inc., Deerfield, IL) and were from the following lot numbers: normal saline 5C869R8; Ringer's lactate, 6C857X4; Plasmalyte-A, 4C837A5;and Plasmalyte-R, 5C935P8.

Functional Measurements

Control hemodynamic measurements and arterial blood samples (a total of 3 ml of blood) were obtained just before hemorrhage, at the end of hemorrhage and before treatment (zero-time), then after hemorrhage at 15 and 30 minutes, 1 through 6 hours on the hour, and at 24 hours if the animal survived. At each of the time points, mean aortic pressure (AP) and heart rate (HR) were obtained with a pressure transducer (Statham Instruments, Inc., Model P23Db, Oxnard, CA) and a physiologic recorder (Gould Brush 2000 Recorder, Gould, Inc., Cleveland, OH). Arterial blood, pH, pO_2, pCO_2, and bicarbonate (HCO_3) were measured (Model 813, pH/Blood Gas Analyzer, Instrumentation Laboratory, Lexington, MA). Arterial blood was also sampled for hematocrit (Hct) and serum lactate (Sigma Technical Bulletin No. 7261-UV).

Autopsy Studies

Most swine living for 24 hours after hemorrhage (survivors) received a standard euthanasia solution. However, one or more survivors in each treatment group were not euthanized until 3 days after treatment and then studied at gross and microscopic levels at autopsy (Table 1). The following tissues were examined histologically: hippocampus and adjacent cerebrum (bilateral),

midbrain, cerebellum (bilateral), brain stem and cervical spinal cord, pituitary gland, adrenal gland, lung (bilateral), heart (right and left ventricles), rectus abdominus muscle, diaphragm, liver, kidney (bilateral), pancreas, stomach, and terminal ileum. In addition, a random unoperated swine from the same animal colony served as a histopathologic control for the instrumented and treated swine.

Data Management and Statistics

For each swine, the following measurement results were recorded in a data base management system: weight (kg) before hemorrhage, hemorrhage time (min), treatment type, treatment time (min), and survival time (min). The following blood and hemodynamic data over the previously described time intervals were also recorded: pH, pCO_2 (torr), pO_2 (torr), HCO_3 (mEq/l), base excess (BE) (mEq/l), serum lactate (mg/dl), Hct(%), mean AP (torr), and HR (beats/min). Swine weight and all of the blood and hemodynamic data were analyzed at each time period with a one-way analysis of variance (ANOVA). Treatment was the independent variable. If a significant F ratio was found, then a multiple comparison (Bonferroni t test) was performed to determine which treatment groups contained the differences. Particular attention was given to the absence of differences at the before hemorrhage-pretreatment (control), and after hemorrhage-pretreatment (zero) periods to insure the reliability of our functional measurements. Survival during the 24-hour observation period after hemorrhage was studied with life-table analysis according to the method of Mantel (8). Significant differences to reject a null hypothesis were defined, a priori, with $P<0.05$ for functional measurement interval data and $P<0.10$ for survival data.

RESULTS

A significant difference was not seen between the weights (kg$\pm$S.D.) of the swine in each treatment group: NS 14 percent=19.1$\pm$1.7, NS 100 percent=20.0$\pm$2.0, NS 300 percent=21.0$\pm$3.0, RL 300 percent=20.1$\pm$2.7, PA=21.3$\pm$2.0, and PR=20.3$\pm$2.1.

Survival rates are depicted in Figure 2 that show improved survival after increasing the percentage of shed blood replaced with NS, i.e. 14 percent, 100 percent, and 300 percent. Survival rate analysis yielded the P-values from the Mantel-Cox statistic listed in Table 3.

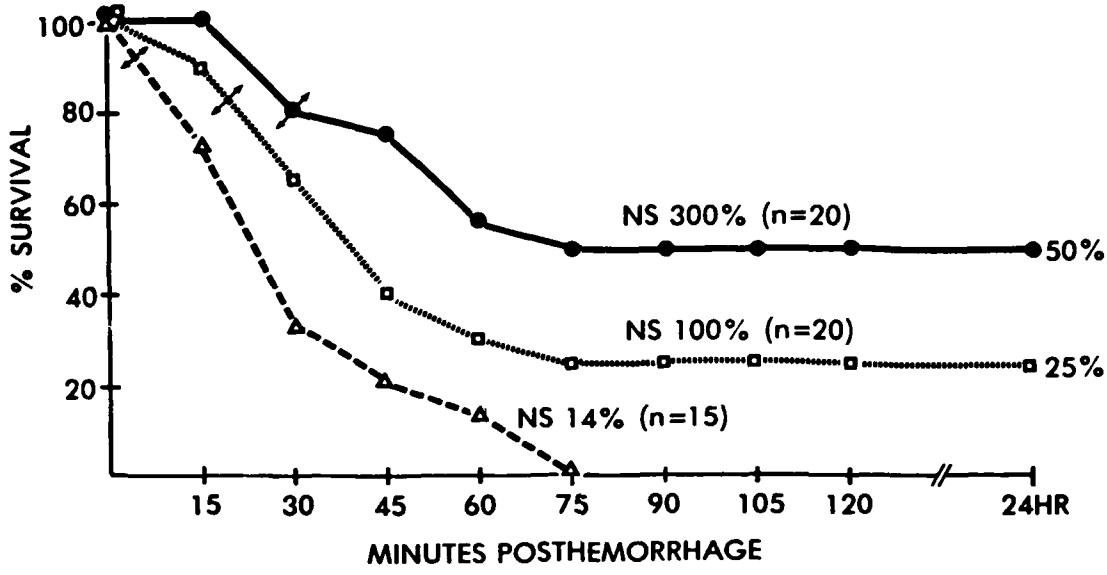

Figure 2. Percent survival after hemorrhage, in minutes, for swine receiving 14%, 100%, and 300% normal (NS) saline replacements for shed blood.

TABLE 3

P values from the Mantel-Cox statistic

Versus	NS 100%	NS 300%	RL	PA	PR
NS 14%	0.02	0.002			
NS 100%		0.07			
NS 300%			0.22	0.37	0.88
RL				0.02	0.10
PA					0.29

A graphic comparison of chemical and hemodynamic measurements, before and after increasing blood replacements with NS, is shown in Figures 3 to 7. The pH, HCO_3, and BE measurements depicted in Figures 3 and 4 were significantly lower in the 14 percent NS treatment group at 15 and 60 minutes. At 60 and 120 minutes, the pH values were significantly lower in the 300 percent NS versus the 100 percent NS groups. In Figure 5 differences were not observed in pO_2 values but pCO_2 levels were significantly lower in the 14 percent NS group at 15 and 30 minutes. Lactate levels were significantly higher in the 14 percent NS group at 30 and 60 minutes while the Hct levels were significantly lower for the 300 percent NS group versus the other two groups at 15 minutes (Figure 6). The Hct of the 100 percent NS group also was significantly lower than the 14 percent NS group at 15 minutes. In Figure 7 the heart rate of the 14 percent NS group was significantly higher than the 100 percent NS and 300 percent NS groups at 15 and 30 minutes. The 300 percent NS group had the highest aortic pressure over the other two groups at the 30 through 90-minute time points (Figure 7).

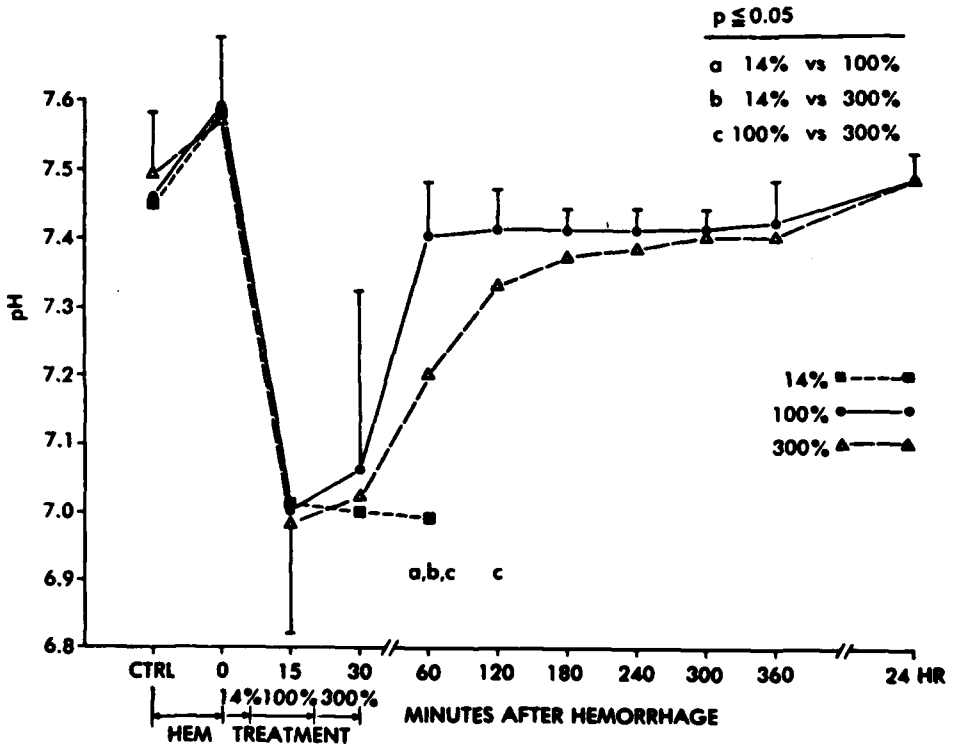

Figure 3. The change in pH from the before hemorrhage control value (CTRL), the end of hemorrhage before treatment (zero) time, and then in minutes after hemorrhage. HEM = hemorrhage. An example of a standard deviation is shown at each time point to avoid obscuring the course of the three lines for each volume replacement (14%, 100%, and 300% = volume of shed blood replaced with normal saline). Significant ANOVA results are shown on the graph.

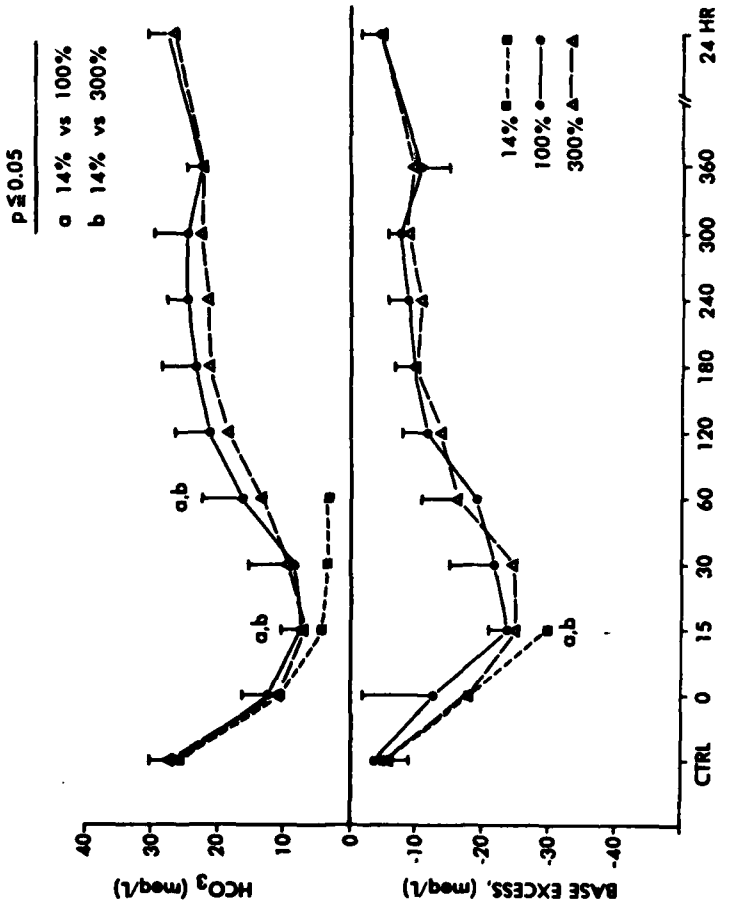

Figure 4. The change in bicarbonate (HCO_3) and base excess concentration in arterial blood. CTRL = control value; HEM = hemorrhage.

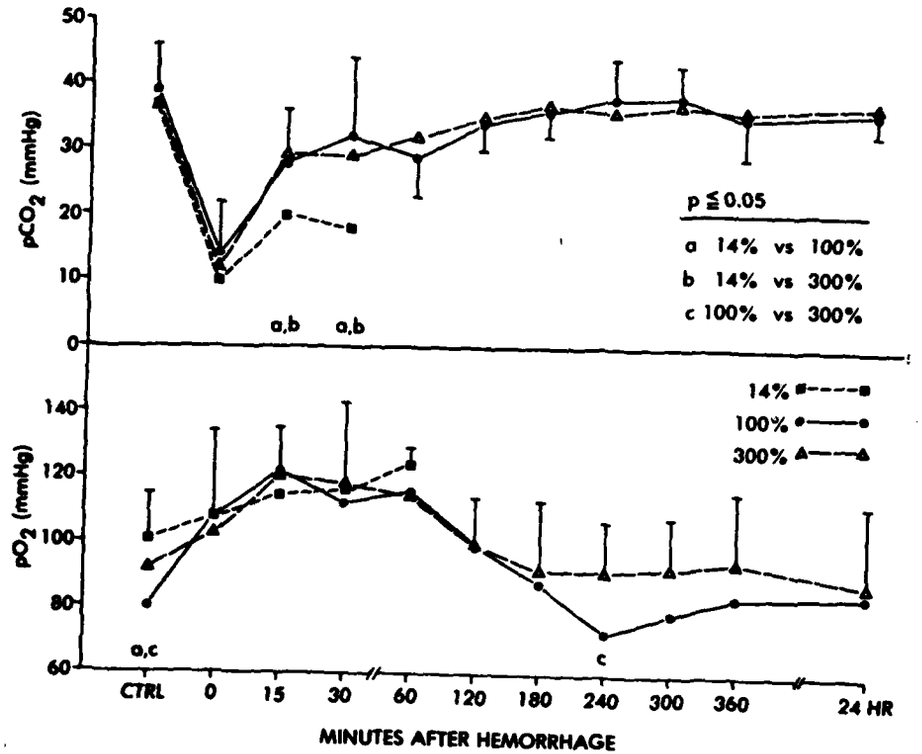

Figure 5. The change in arterial blood gases over time. CTRL = control value. HEM = hemorrhage.

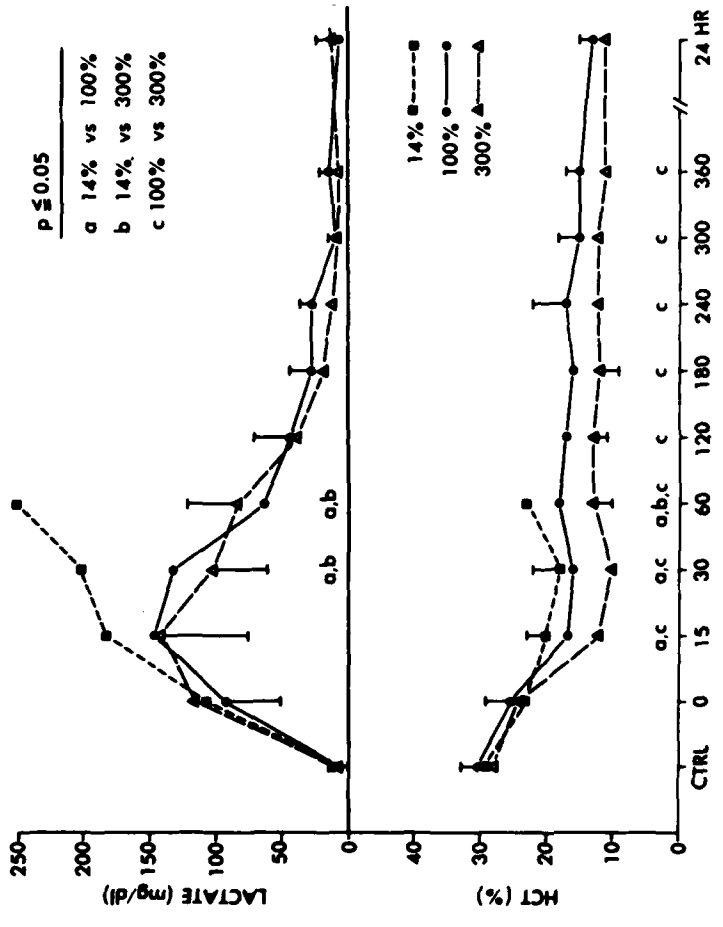

Figure 6. The change in arterial lactate and hematocrit (Hct) over time. CTRL = control value. HEM = hemorrhage.

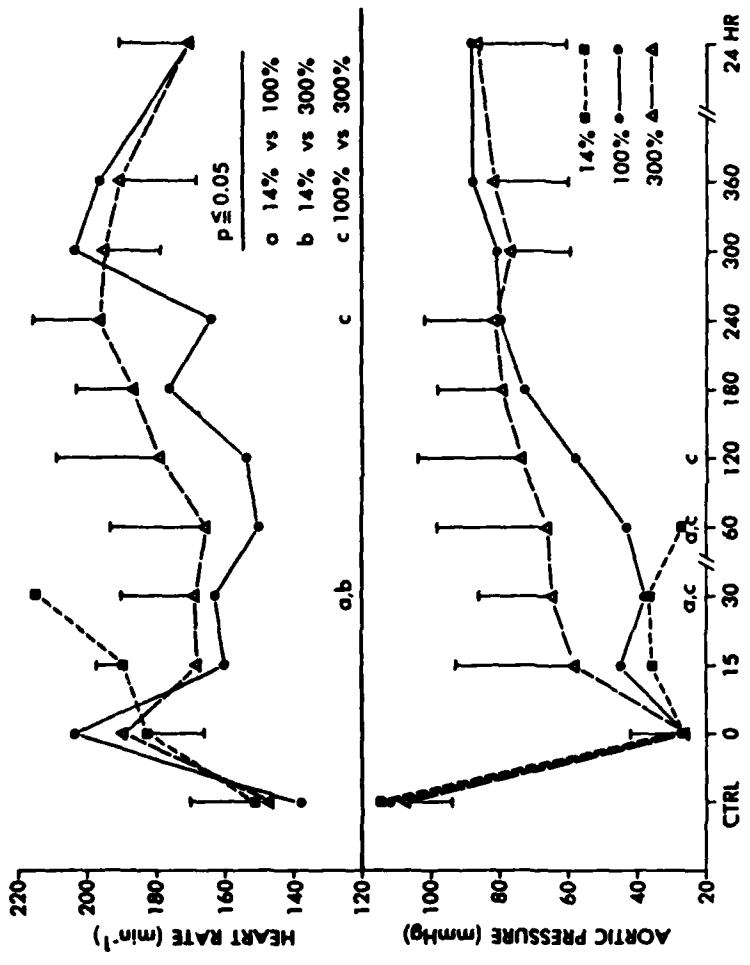

Figure 7. The change in aortic pressure and heart rate over time is shown. CTRL = control value. HEM = hemorrhage.

A comparison of survival rates is shown in Figure 8 after 300 percent replacement of shed blood in 30 minutes with the four crystalloid solutions. RL exhibited the best 24-hour survival rate (67%). Comparison of the survival curves for all 300 percent treatments with the Mantel - Cox statistic yielded the P-values listed in Table 3.

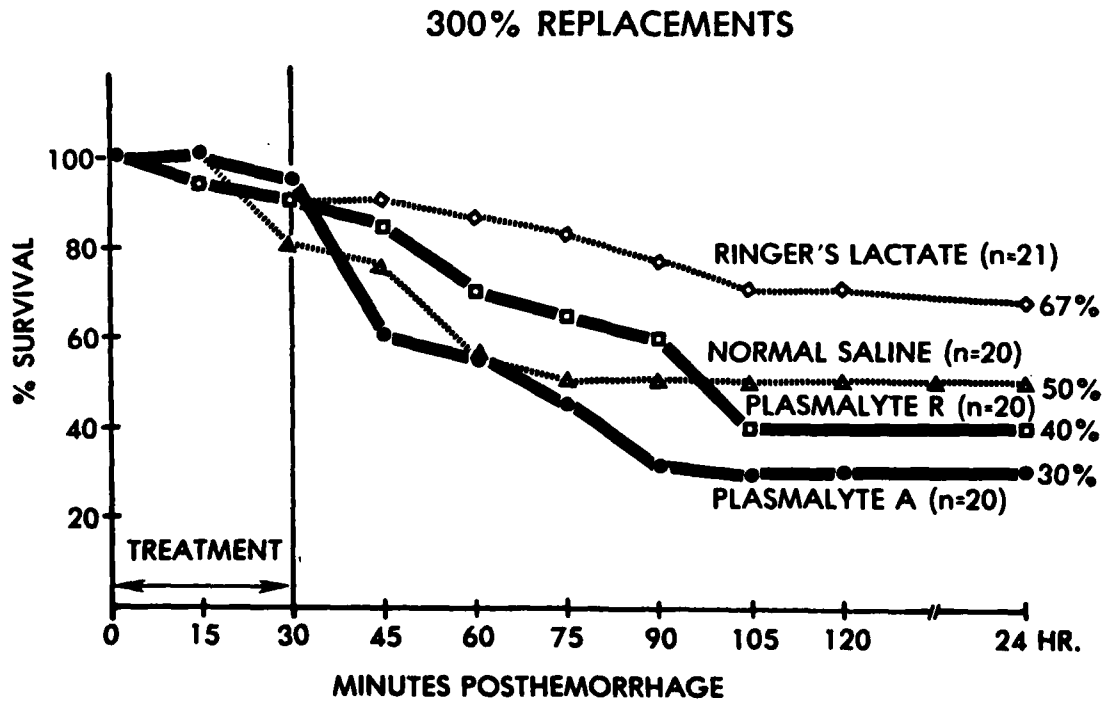

Figure 8. After hemorrhage, the per cent survival in minutes is shown for the 300% replacement of shed blood. The vertical line represents the end of treatment.

Results of chemical and hemodynamic measurements are shown in Figures 9 to 13 for the 300 percent replacement solutions and the numeric data for these figures are listed in Table 4 and 5. Reliable blood gas analysis for the PR group could not be obtained because of blood gas analyzer mechanical problems during that study period. In Figures 9 and 10, the RL and PA treatment groups resulted in significantly higher pH, HCO_3, and BE values than the NS 300 percent group at 15 minutes and at the 120 through 360-minute time points. In Figures 11 and 12 significant differences were not observed in pO_2, pCO_2, and Hct values. In Figure 12 the lactate values at 60 and 120 minutes were significantly higher in the PR group. In Figure 13 between-group differences were not observed in heart rate or aortic pressure.

Among the surviving animals studied at autopsy 3 days after hemorrhage, gross and microscopic autopsy differences were not found in the tissues examined regardless of the treatment. Pathologic differences were not found when experimental swine were compared to control swine.

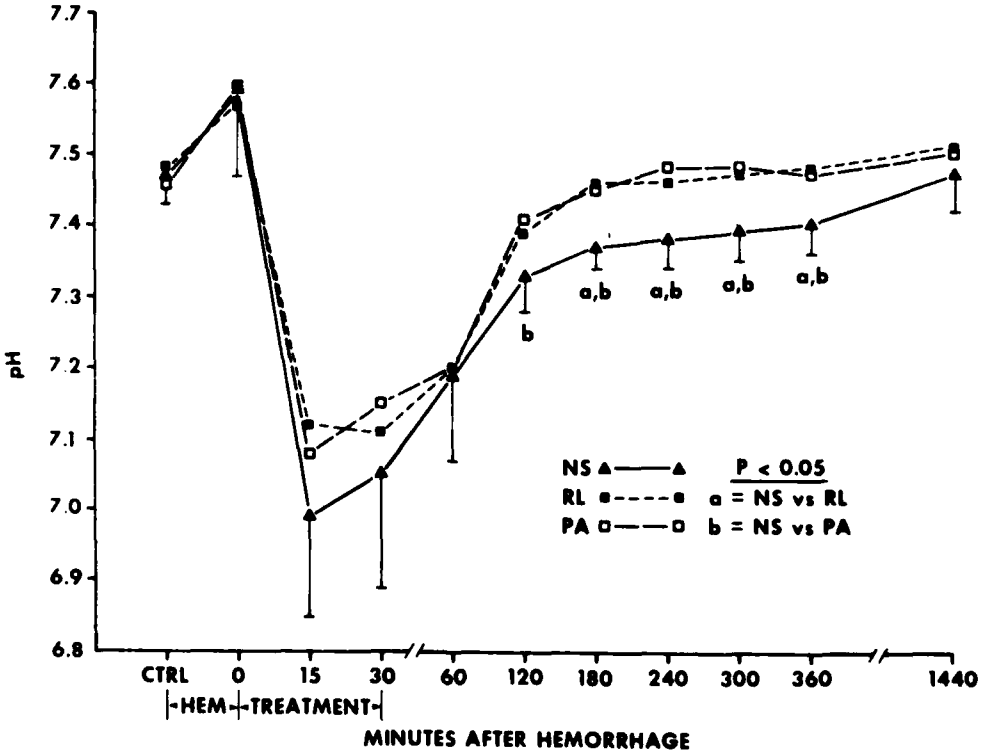

Figure 9. Changes in pH from the before hemorrhage control value (CTRL), the end of hemorrhage before treatment (zero) time, and then in minutes after hemorrhage. HEM = hemorrhage. Representative standard deviations are shown to avoid obscuring the course of the four lines for each 300% replacement solution. Significant ANOVA results are depicted on the graph. NS = normal saline, RL = Ringer's lactate, PA = Plasmalyte A.

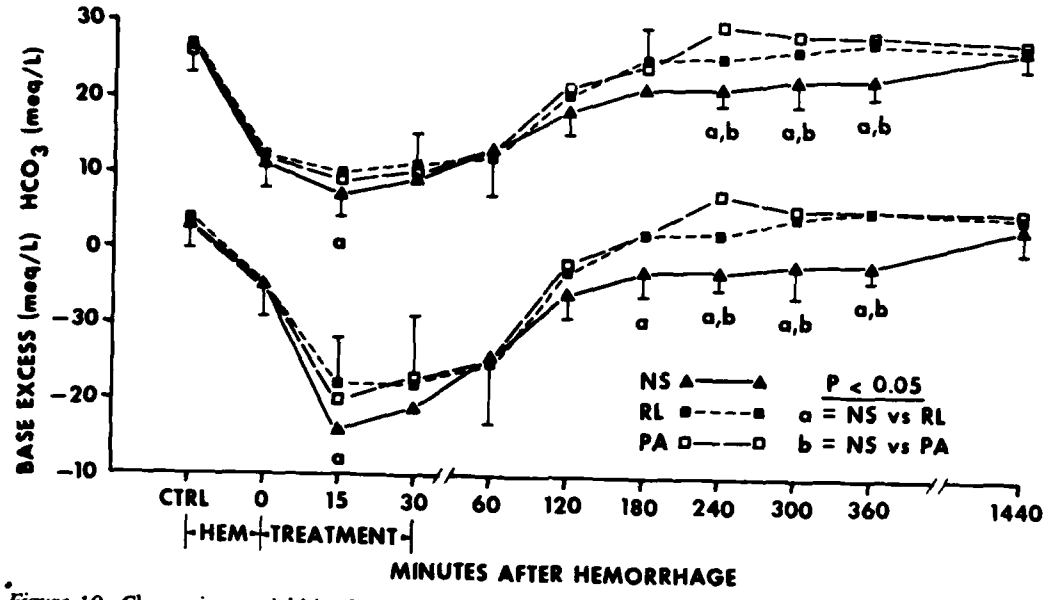

Figure 10. Change in arterial bicarbonate (HCO_3) and base excess concentration from the before hemorrhage control value (CTRL), the end of hemorrhage before treatment (zero) time, and then in minutes after hemorrhage. HEM = hemorrhage. Representative standard deviations are shown to avoid obscuring the course of the four lines for each 300% replacement solution. Significant ANOVA results are depicted on the graph. NS = normal saline, RL = Ringer's lactate, PA = Plasmalyte A.

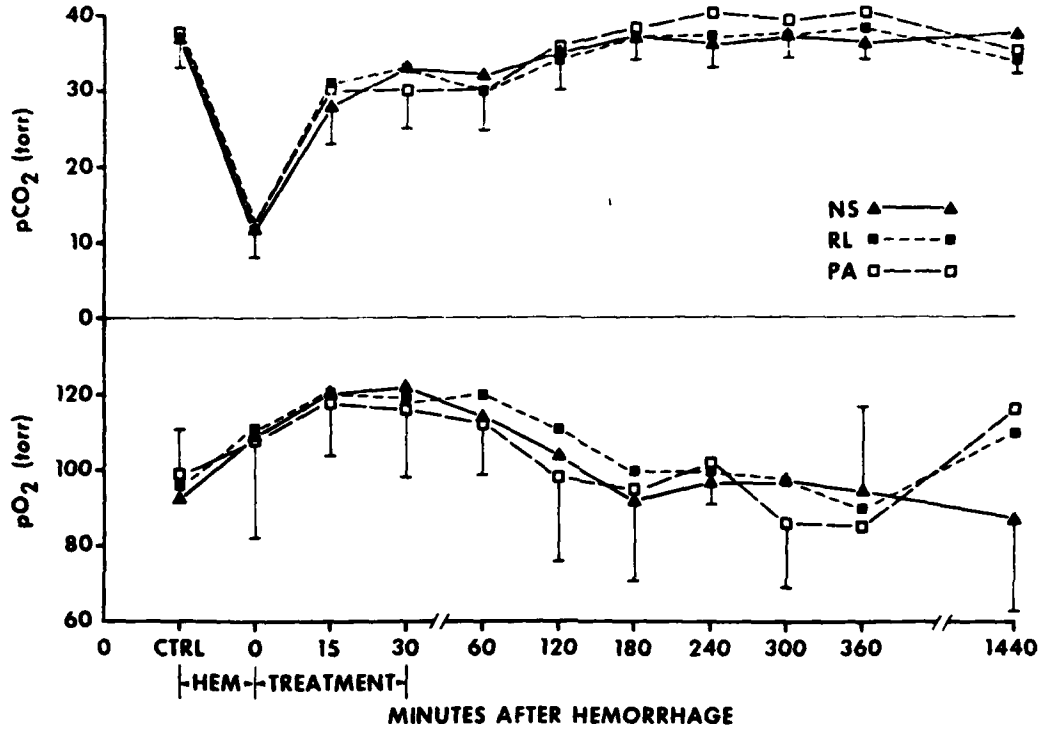

Figure 11. The change in arterial blood gases from the before hemorrhage control value (CTRL), the end of hemorrhage before treatment (zero) time, and then in minutes after hemorrhage. HEM = hemorrhage. Representative standard deviations are shown to avoid obscuring the course of the four lines for each 300% replacement solution. Significant ANOVA results are depicted on the graph. NS = normal saline, RL = Ringer's lactate, PA = Plasmalyte A.

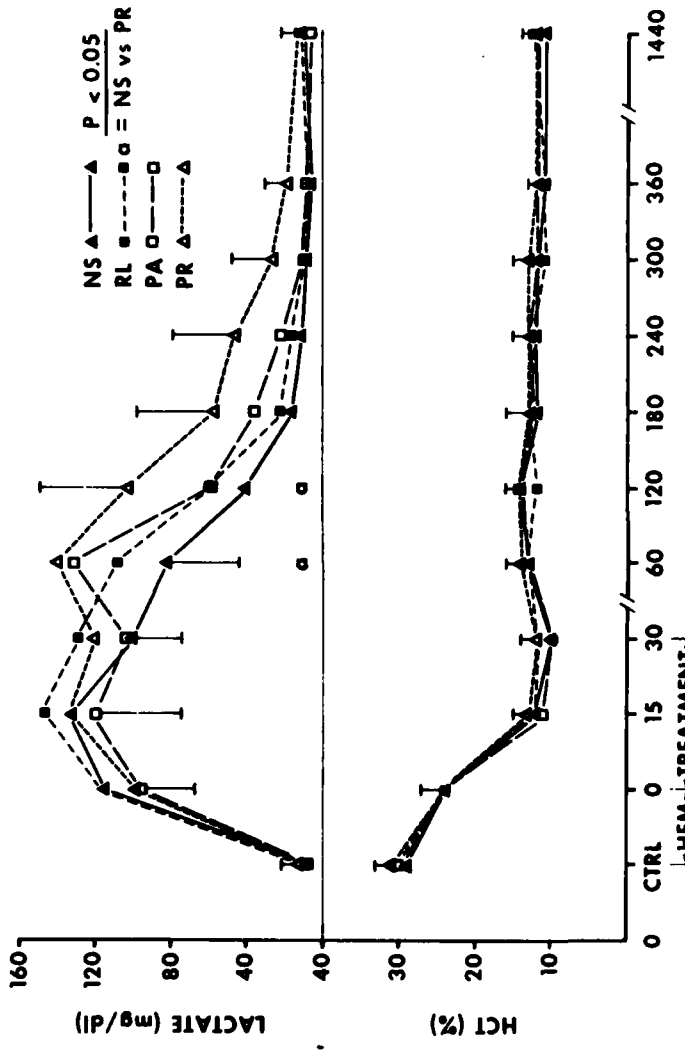

Figure 12. The change in arterial blood lactate and hematocrit (Hct) from the before hemorrhage control value (CTRL), the end of hemorrhage before treatment (zero) time, and then in minutes after hemorrhage. HEM = hemorrhage. Representative standard deviations are shown to avoid obscuring the course of the four lines for each 300% replacement solution. Significant ANOVA results are depicted on the graph. NS = normal saline, RL = Ringer's lactate, PA = Plasmalyte A, PR = Plasmalyte R.

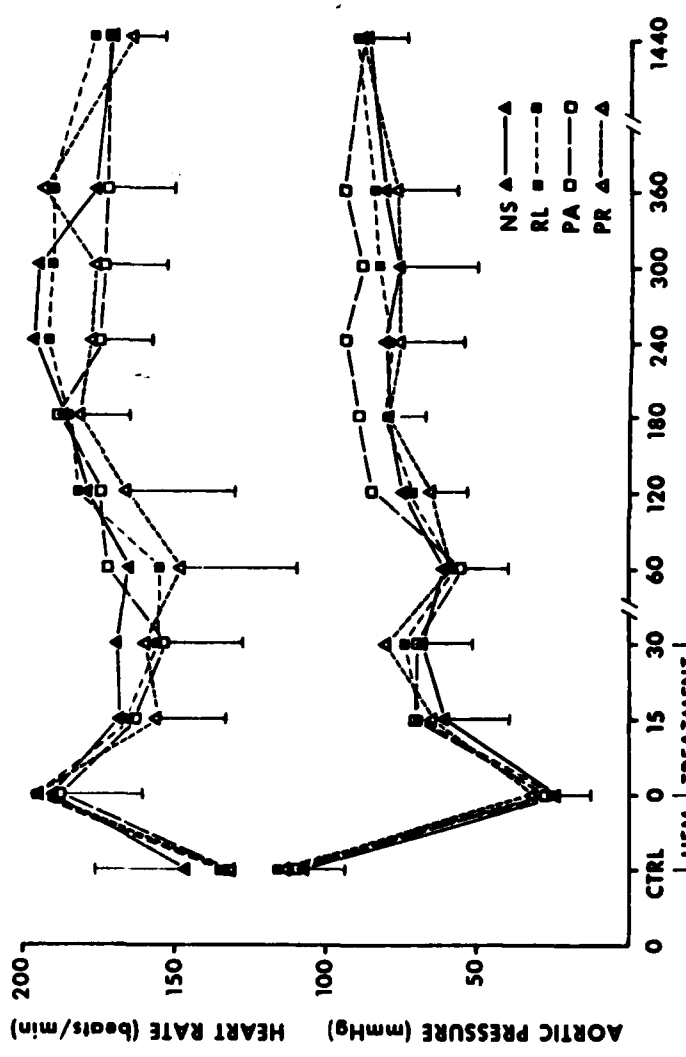

Figure 13. The change in the hemodynamic variables of mean aortic pressure and heart rate from the before hemorrhage control value (CTRL), the end of hemorrhage before treatment (zero) time, and then in minutes after hemorrhage. HEM = hemorrhage. Representative standard deviations are shown to avoid obscuring the course of the four lines for each 300% replacement solution. Significant ANOVA results are depicted on the graph. NS = normal saline, RL = Ringer's lactate, PA = Plasmalyte A, PR = Plasmalyte R.

Table 4: Arterial Blood Gas Data (Mean ± Standard Deviation)

		MINUTES AFTER HEMORRHAGE									
FLUID	CTRL	0	15	30	60	120	180	240	300	360	1440
pH											
NS	7.47±.04	7.59±.10	6.99±.14	7.05±.16	7.19±.12	7.33±.05	7.37±.03	7.38±.04	7.39±.04	7.40±.04	7.47±.05
RL	7.48±.03	7.57±.10	7.12±.12	7.11±.16	7.20±.17	7.39±.09	7.46±.04	7.46±.05	7.47±.06	7.48±.03	7.51±.04
PA	7.46±.03	7.59±.13	7.08±.16	7.15±.15	7.20±.24	7.41±.03	7.45±.06	7.48±.04	7.48±.04	7.47±.04	7.50±.04
p<0.05						b	a,b	a,b	a,b	a,b	
pCO_2 (torr)											
NS	37±4	12±4	28±5	33±4	32±2	35±3	37±3	36±3	37±3	36±2	37±2
RL	37±4	12±4	31±5	33±4	30±5	34±4	37±2	37±3	37±4	38±4	34±2
PA	38±4	12±4	30±5	30±5	30±9	36±3	38±3	40±6	39±2	40±2	35±3
pO_2 (torr)											
NS	92±8	109±24	121±13	122±13	114±5	104±9	92±21	97±6	97±13	95±22	88±25
RL	96±12	111±16	121±13	119±15	120±14	111±14	100±15	100±10	97±9	90±18	110±14
PA	99±12	108±26	118±14	116±18	112±13	98±22	95±19	102±23	86±17	85±20	116±20
HCO_3 (mEq/liter)											
NS	27±3	11±3	7±3	9±3	13±4	18±3	21±2	21±2	22±3	22±2	26±2
RL	27±3	12±5	10±3	11±4	12±5	20±5	25±4	25±3	26±3	27±3	26±3
PA	26±3	12±3	9±3	10±4	13±8	21±3	24±4	29±5	28±1	28±2	27±3
p<0.05			a					a,b	a,b	a,b	
BE (mEq/liter)											
NS	3±3	-5±4	-24±6	-21±6	-14±6	-6±3	-3±3	-3±2	-2±4	-2±2	3±3
RL	4±4	-5±5	-18±6	-18±7	-15±8	-3±6	2±4	2±4	4±4	5±3	4±4
PA	3±4	-5±4	-20±7	-17±8	-15±11	-2±3	2±3	7±4	5±2	5±3	5±3
p<0.05			a				a	a,b	a,b	a,b	

CTRL=Control a=NS vs RL b=NS vs PA

Table 5: Lactate, Hematocrit, Aortic Pressure, and Heart Rate Data (Mean ± Standard Deviation)

		MINUTES AFTER HEMORRHAGE									
FLUID	CTRL	0	15	30	60	120	180	240	300	360	1440
Lactate (Mg/dl)											
NS	8±5	115±32	132±30	101±26	82±39	41±23	17±12	11±8	8±4	7±4	11±11
RL	9±4	119±32	146±42	128±33	109±49	22±14	22±14	16±14	12±8	9±5	10±6
PA	7±3	96±28	120±45	103±35	130±59	58±30	35±22	22±17	10±5	9±3	7±2
PR	13±10	98±28	133±28	120±35	139±47	102±47	57±41	47±31	27±21	20±11	12±9
p<0.05					a	a					
Hematocrit (%)											
NS	29±3	24±3	12±1	10±1	13±2	14±2	12±1	12±1	12±1	11±1	11±2
RL	30±3	24±2	12±2	12±2	13±2	12±2	13±3	12±2	11±1	11±1	12±2
PA	30±2	24±2	11±2	10±2	13±2	14±1	13±2	13±1	12±1	12±1	12±1
PR	31±2	24±3	13±2	12±2	14±2	14±2	13±1	13±2	13±2	12±1	12±2
Aortic Pressure (Torr)											
NS	108±14	24±11	61±20	68±17	62±14	74±11	79±12	82±8	77±12	82±6	87±13
RL	117±15	25±9	70±19	74±17	58±18	72±15	77±9	79±11	83±8	85±7	90±17
PA	110±15	28±8	71±15	69±18	56±16	85±16	89±12	94±14	88±7	94±9	88±15
PR	114±12	32±8	66±14	81±14	58±11	65±11	79±11	76±19	77±25	77±19	88±18
Heart Rate (beats/min)											
NS	147±30	190±16	168±35	169±22	165±32	179±31	187±18	197±13	195±18	176±23	170±24
RL	135±14	195±22	164±31	156±18	154±24	183±19	186±22	192±19	191±19	190±22	176±21
PA	132±18	187±27	163±24	153±25	172±25	174±28	189±18	174±17	173±21	172±21	171±19
PR	131±16	196±37	155±22	159±25	147±38	166±36	182±16	177±16	176±21	193±16	163±10

CTRL=Control a=NS vs PR

DISCUSSION

The objective of the first portion of this study was to compare the responses of the unanesthetized swine model to increasing blood replacements with normal saline after an otherwise fatal hemorrhage. The survival rates and functional measurements could then be compared to the results of the second portion of this study which dealt with a comparison ofqual volumes of various crystalloid solutions.

The swine weights were not different between treatment groups. This observation is especially important when estimating blood volume by weight for fixed volume removal because in our experience, regardless of treatment, most animals less than 14 kg will live while most swine over 25 kg will die after this hemorrhage method. Rigid adherence to the weight range in this study is mandatory to achieve reproducibility in the volume of blood removed rather than reliance on formulas to estimate blood volume for a wide variety of weights.

The survival rates illustrated in Figure 2 were obtained with two experimental variables: increasing volumes of the same resuscitation solution (normal saline) and increasing rates of administration (to a maximum rate of 6 ml/kg/min). In our experience, a rate of 9 ml/kg/min was associated with death due to acute fluid overload. The survival rate increased with each incremental increase of volume and rate of blood replacement. Increasing volume replacement with NS was reflected adequately between groups in Hct (Figure 6). These results are not surprising: adequate and rapid volume replacement is important to promote survival during resuscitation for severe hypovolemia.

The survival curves (Figure 2) indicate that if an animal survived for 75 minutes after hemorrhage then the swine would survive throughout the period of observation. Indeed all animals observed for up to 3 days after hemorrhage were normal by histopathologic examination. Late deaths did not occur. This injury-to-death interval of 75 minutes in the swine model mimics the interval in human trauma (1) and supports a saying among trauma surgeons that "trauma deaths occur right away or days to weeks later." Traditionally, hemorrhagic shock has been studied with heparinized, anesthestized, fixed-pressure animal models that have a survival time of four to six hours (9). These models do not duplicate the scenario of the trauma patient or the survival interval from injury to death nearly as well as the swine model used in this study.

Deaths occurred within 75 minutes after hemorrhage. What hemodynamic or blood measurement reflected a fatal outcome during this period? The measurements of the 14 percent replacement group obtained during the 75 minutes after hemorrhage were obviously different from the 100 percent and 300 percent replacement groups in Figures 3 to 7. The 14 percent group was characterized by a significantly lower pH, HCO_3, BE, pCO_2, and AP plus a higher lactate level, Hct, and HR. All these easily discernible differences were associated with

significantly different survival curves between the 14 percent NS versus the 100 percent NS or 300 percent NS groups. The swine of the 14 percent group with inadequate volume resuscitation and acidosis maintained a higher ventilatory effort to keep the pCO_2 less than 20 torr (Figure 5). Death in these swine first involved respiratory arrest followed by cardiac standstill several minutes later.

A statistical comparison of data from the 100 percent and 300 percent NS replacement groups within the 75-minute hemorrhage-to-death interval revealed no significant between-group differences in HCO_3, BE, pCO_2, pO_2, lactate, or HR. The 100 percent group had a significantly higher pH at 60 and 120-minutes (Figure 3) than the 300 percent group, even though at these time points AP was significantly lower in the 100 percent group (Figure 7). The increased blood pressure, presumably due to the increased volume replacement of the 300 percent group, evidently was not able to overcome the acidifying effect of an increased chloride load (10). The lower pH of the 300 percent NS group might be due to a "dilutional acidosis." The higher chloride concentration of NS, as compared to plasma, displaced other anions, principally HCO_3 (11). However, despite the more favorable pH for the 100 percent group, AP was the only measurement that predicted the 25 percent between-group difference in survival.

The second objective of this study was to compare equal volumes of NS and three different crystalloid solutions containing water, electrolytes, and potential bicarbonate sources (Table 2). The potential bicarbonate sources of these crystalloid solutions are sodium lactate, gluconate, or acetate, however, all can be metabolized to glycogen in the presence of oxygen leaving a sodium ion in the extracellular fluid as sodium bicarbonate. The addition of magnesium to PA and PR is thought to mimic the electrolyte profile of the lost plasma. The need for magnesium during severe hypovolemia is unclear. Calcium was excluded in PA so that blood can be infused through an administration tubing containing PA without clot formation. When these solutions were given in equal volumes over equal times, RL provided the best survival rates over NS 300 percent, and even more so over PR and PA (Figure 8). A significant difference between the survival curves of RL and PA was found (Table 3).

The superior survival associated with RL over PA, PR, and NS was not attributable to differences in the volume of resuscitation fluid. Indeed the AP, HR, and Hct were essentially the same for all treatment groups at all times before, during, or after treatment (Figures 12, 13). The survival differences were not attributable to a better acid base status in the RL swine. During and after a 105 minute hemorrhage to death period (Figure 8), RL and PA showed similar acid base values while both were better than NS 100 percent (Figures 9, 10). We feel the increased chloride load of NS, as compared to PA and PR, accounts for the trend to lower pH, HCO_3, and BE values of the NS 300 percent group during treatment (Figures 9, 10 at the 15-minute interval). The lower pH, HCO_3, and BE relationship reappeared from 120 to 360 minutes

and was statistically significant with respect to pH (Figures 9, 10). The higher pH 2 hours after hemorrhage in the RL and PA groups was probably due to HCO_3 production from lactate, acetate, or gluconate in the surviving animals. These potential bicarbonate sources would not be expected to act upon pH during the treatment period (0 to 30 minutes after hemorrhage) in this study because they are not capable of immediate buffering in vitro (12). Therefore during the 1-hour period after hemorrhage, when survival was determined in our swine, the bicarbonate sources of RL were unlikely to contribute HCO_3 and account for the improved RL survival.

The conversion of sodium lactate to sodium bicarbonate in normal man requires 1 to 2 hours in the presence of oxygen (13). The peak production of HCO_3 in normovolemic dogs occurs after 80 minutes of acetate infusion and after 180 minutes of lactate infusion (14). Gluconate infusion was not associated with an increase in plasma HCO_3 (14). More bicarbonate appears to be produced from acetate than lactate in dogs (14) but this may be due to the racemic mixture of d- and l-lactate. Only a fraction of sodium lactate is converted to bicarbonate. All of the l-lactate while only 20 percent of the d-lactate is oxidized (13). Perhaps the reasons for the popularity of Ringer's acetate in Scandinavian countries are this difference in potential bicarbonate production from acetate and lactate and the illogical addition of lactate to an organism already in lactic acidosis. Hartmann and Senn (13) originally placed the lactate in Ringer's solution to provide a delayed source of bicarbonate since the administration of sodium bicarbonate to patients with metabolic acidosis frequently was associated with rapid shifts of pH to an uncompensated alkalosis. We can conclude that the potential bicarbonate sources in RL and PA did not contribute to survival because plasma HCO_3 levels were similar in the PA and RL group and significantly different survival rates were observed between these two treatment groups. The most important contribution to survival by the bicarbonate sources in RL, PA, and PR may be to decrease the chloride concentration from that of NS.

Differences in the ion constituents of the crystalloid solutions used in this study might contribute to the poor survival rates of swine receiving PA and PR. The ions common to PA and PR, but not RL may be deleterious to survival. The comparisons in Table 2 disclose that the only ions present in PR and PA but not in RL are magnesium and acetate. Magnesium can control and regulate the entry and exit of calcium in vascular smooth muscle (15). A slight excess of magnesium resulted in bradycardia in man (16). Indeed a dose-related negative chronotropic effect of magnesium has been observed in atrial or ventricular preparations (17). In rabbit atria, magnesium-induced bradycardia can be decreased with addition of an equimolar quantity of calcium (18). PR contains approximately equal concentrations of calcium (5 mEq/l) and magnesium (3 mEq/l). However, we did not see bradycardia in our animals during or after treatment with PA or PR as compared to RL-treated swine. The survival curve of PR between 30 and

45 minutes after hemorrhage (Figure 8) was improved slightly over the PA curve. Possibly this improvement was due to the presence of calcium in PR. Magnesium is a vasodilator in the dog forelimb while calcium is a vasoconstrictor (19). Perhaps magnesium, especially in the absence of calcium, as in PA, should be avoided in a resuscitation solution used for rapid volume expansion following severe blood loss. However, the hemodynamic evidence of our study is not convincing and the quantities of magnesium administered were small.

The vascular effects of the gluconate in PA are unknown but isotonic sodium acetate is a vasodilator in the dog extremity (19,20) and in isolated arteries and veins from the rat (21). Acetate induced constriction of rat mesenteric arterioles and venules (22). Our hemodynamic data of AP and HR (Figure 13) did not indicate any differences among the RL, PA, and PR groups indicative of changes in vascular resistance during or after treatment. However, AP and HR measurements may have been insensitive to important regional vascular resistance changes. Lactate elevations are observed in the PA and PR treated groups and may be metabolic indicators of a regional change in vascular resistance and resultant tissue ischemia. In Figure 12 the RL and NS groups showed a lactate peak at 15 minutes and then a steady decline. The lactate peak of the PA and PR groups was similar and these levels began a decline during treatment but rose again at 30 minutes. The lactate levels of the PR group were elevated significantly above the NS group. These results must be considered with caution because PR (as well as RL) contains a small amount of sodium lactate (90 mg/dl). Swine treated with PR received a total of approximately 320 mg of sodium lactate. However this constraint would not explain the same lactate peak observed 30 minutes after treatment with a lactate-free PA solution. Conceivably, the acetate load given during PA and PR treatment may have caused mesenteric vasoconstriction or skeletal vasodilation and decreased tissue perfusion leading to increased lactate levels at a time after hemorrhage when survival is determined. Understanding the effects of acetate on regional tissue perfusion during severe hemorrhage may be beneficial in determining the reason for poorer survival of PR- or PA-treated swine relative to RL-treated swine.

By monitoring physiological values in a conscious swine model that simulates survival commonly seen in human trauma after rapid hemorrhage, we studied the effects of four crystalloid blood replacement solutions. The increased chloride load of NS promoted acidosis when administered in a volume sufficient to elevate AP and promote survival. The same volume of NS that promoted survival was used to compare three other crystalloid solutions containing potential bicarbonate sources. RL provided the best survival over NS, PA, and PR. Of the four crystalloid solutions, PA and PR resulted in the lowest survival rates. RL may have been the best crystalloid solution to promote survival in this study because of its decreased chloride concentration (as compared to NS) and the absence of acetate (compared to PA and PR).

CONCLUSIONS

Compared to acetate and/or magnesium containing crystalloid resuscitation solutions, Ringer's lactate is the best agent to prevent death after an otherwise lethal and clinically relevant hemorrhage. Ringer's lactate is the superior solution because of its decreased chloride load (as compared to normal saline) and because of the absence of acetate and magnesium (as compared to Plasmalyte-A and Plasmalyte-R).

RECOMMENDATION

Ringer's lactate should be the cystalloid resuscitation agent of choice for treatment of combat casualties suffering from potentially fatal blood loss.

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