

Effect of hypertonic vs isotonic saline solution on responses to sublethal *Escherichia coli* endotoxemia in horses

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SUMMARY

Cardiovascular responses to sublethal endotoxin infusion (*Escherichia coli*, 50 µg/ml in lactated Ringer solution at 100 ml/h until pulmonary arterial pressure increased by 10 mm of Hg) were measured 2 times in 5 standing horses. In a 2-period crossover experimental design, horses were either administered hypertonic (2,400 mosm/kg of body weight, IV) or isotonic (300 mosm/kg, IV) NaCl solution after endotoxin challenges. Each solution was administered at a dose of 5 ml/kg (infusion rate, 80 ml/min). Complete data sets (mean arterial, central venous, and pulmonary arterial pressures, pulmonary arterial blood temperature, cardiac output, total peripheral vascular resistance, heart rate, plasma osmolality, plasma concentration of Na, K, Cl, and total protein, blood lactate concentration, and PCV) were collected at 0 (baseline, before endotoxin infusion), 0.25, 1, 1.5, 2, 2.5, 3, 3.5, 4, and 4.5 hours after initiation of the endotoxin infusion. Blood constituents alone were measured at 0.5 hour and cardiovascular variables alone were evaluated at 0.75 hour. By 0.25 hour, endotoxin infusion was completed, a data set was collected, and saline infusion was initiated. By 0.75 hour, saline solutions had been completely administered.

Mean (\pm SEM) cardiac output decreased (99.76 ± 3.66 to 72.7 ± 2.35 ml/min/kg) and total peripheral resistance (1.0 ± 0.047 to 1.37 ± 0.049 mm of Hg/ml/min/kg) and pulmonary arterial pressure (33.4 ± 0.86 to 58.3 ± 1.18 mm of Hg) increased for both trials by 0.25 hour after initiation of the endotoxin infusion and prior to fluid administration. For the remainder of the protocol, cardiac output was increased and total peripheral resistance was decreased during the hypertonic, compared with the isotonic, saline trial. Cardiac output was decreased and total peripheral resistance was increased during the isotonic saline trial, compared with baseline values. Both trials were associated with increased blood lactate concentra-

tion, but lactate values during the isotonic saline trial were greater and remained increased above baseline values for a longer period (4 hours) than during the hypertonic saline trial (2.5 hours). It was concluded for this model of endotoxemia, that IV administered hypertonic saline solution was associated with more-desirable cardiovascular and metabolic responses than was an equal volume of isotonic saline solution.

Maintenance of peripheral perfusion is essential to any therapeutic regimen for treatment of endotoxic shock. In the past, this strategy has relied on use of large volumes of isotonic fluids.¹ However, in animals with experimental and clinical hemorrhagic shock, small-volume (5 to 10 ml/kg of body weight) hypertonic (600 to 2,400 mosm/kg) saline infusion has been associated with greater and more-prolonged improvement in cardiopulmonary function and survival than treatment with isotonic solutions.²⁻⁸ In an experimental model of lethal hemorrhage, 7.5% saline solution was superior in supporting cardiovascular and metabolic function and was associated with greater survival rates than iso- or other hypertonic saline formulations.⁵

In animal models of hypovolemic shock, the administration of hypertonic solutions is associated with decreased total peripheral, pulmonary, and coronary arterial resistances and increased cardiac output.^{2,3,5-8} Cellular protective effects and direct improvement of myocardial performance have also been attributed to hypertonic solution administration during hypovolemic shock.^{9,10} The mechanisms associated with these desirable responses are unclear. It has been postulated that most of the infused sodium remains in the extracellular space and acts as an effective osmole, increasing intravascular volume by intracellular fluid extraction.^{4,11,12} However, cardiovascular responses associated with hypertonic saline solution seem dependent on a reflex arc, which includes afferent and efferent neurons, vagal tracts, and unknown pulmonary osmoreceptors.^{2,3} The IV administration of hypertonic solutions is associated with an increase in plasma osmolality and changes in microvascular and systemic circulation that are more accentuated and prolonged than those after infusion of the same fluid intra-arterially or passed through denervated lungs.^{2,13-15} Similar im-

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provements in cardiovascular function and survival are associated with hypertonic saline administration in models of endotoxic shock in dogs.^{16,17}

Models of endotoxemia in horses have relied on fixed doses of endotoxin, regardless of well-categorized variations in individual responses and effects of specific endotoxin.^{18,19} In contrast, many studies of hemorrhagic shock control for individual variation in response to volume removed by bleeding to effect.^{2-6,12-13,15} To improve comparison between experimental designs and manipulations of endotoxemia, dose-to-effect models may be appropriate. The purpose of the study reported here was to evaluate the effects of hypertonic vs isotonic saline solution on responses to a sublethal dose-to-effect model of *Escherichia coli* endotoxemia in horses.

Materials and Methods

Horses—Cardiovascular, pulmonary arterial blood temperature and blood constituent measurements were assessed in 5 healthy adult geldings subjected to IV administration of sublethal doses of *Escherichia coli* endotoxin.^a Horses weighed between 386.3 and 463.6 kg (mean \pm SEM, 415.3 \pm 8.38 kg) for both trials. Ages were approximate and ranged from 3 to 9 years (4.8 \pm 0.38 years). Horses were selected on the basis of good health, tractability, and response to prolonged restraint in large-animal stocks. Horses were trained to stand quietly in stocks for at least 4 hours.

Environment—All procedures were performed in an isolated area, with the temperature controlled to 21 \pm 1 C. Horses were kept in large-animal stocks for the entire trial. Grass hay and water were offered ad libitum throughout all procedures.

DATA COLLECTION

A complete data set included mean arterial, central venous, and pulmonary arterial pressures, pulmonary arterial blood temperature, cardiac output, total peripheral resistance, heart rate, plasma osmolality, plasma concentration of Na, K, Cl and total protein, blood lactate concentration, and PCV.

Cardiac output—Cardiac output determinations were performed, using described procedures,²⁰ with the following exceptions. Forty milliliters of cold 5% dextrose solution^b was administered within 2 seconds, using a power injector.^c To control for respiratory effects on cardiac output, the dextrose solution was injected into the right atrium shortly after expiration. The temperature of the dextrose solution was assumed to be the temperature of the ice bath in which the solution was kept throughout the study. The dextrose injectate, ice bath, and injector were kept cooled in a temperature-controlled freezer^d to decrease heat accumulation. Thermodilution curves were gener-

^a Lipopolysaccharide from *Escherichia coli* 055:B5; phenol extract, Sigma Chemical Co, St Louis, Mo.

^b 5% Dextrose injection USP (5% dextrose in water), Travenol Laboratories, Deerfield, Ill.

^c Thermodilution injector for horses, Columbus Instruments Corp, Columbus, Ohio.

^d Whirlpool Corp, Benton Harbor, Mich.

ated^e and stored^f for later evaluation. The average of 3 thermodilution curves was used to calculate cardiac output for each data set. Only gamma-variate curves with a figure of merit of ≥ 0.90 were accepted for analysis. Cardiac output determination was then divided by individual body weight (kilograms) to correct for weight differences between horses.

Venous and arterial pressure and blood temperature measurements—At least 30 days prior to the trials, a right carotid exteriorization was performed on all horses.²¹ All areas of catheter and suture placement were aseptically prepared, and local anesthesia was provided, using 0.75% bupivacaine.^g An 18-gauge catheter^h was placed into the right exteriorized carotid artery and used for direct arterial pressure measurements. A 10-gauge catheterⁱ was used to introduce an 8-F catheter^j into the left jugular vein at a cranoventral cervical site. The catheter^j tip was directed into the right atrium and was used for central venous pressure measurements and for administration of cold solution^b for thermodilution cardiac output measurements. A 10-gauge catheter^j tip was placed in the left jugular vein in a caudocervical site and the end of a thermodilution catheter^k was directed through it and into the pulmonary artery. The thermodilution catheter^k was used for pulmonary arterial pressure and blood temperature measurements. Vascular pressure measurements were recorded continuously.^l

Total peripheral resistance—Total peripheral resistance (mm of Hg/ml/min/kg) was calculated for each period in which cardiovascular measurements were obtained.²²

Blood and urine constituent and indices calculations—Samples for serum, plasma, and blood analysis were collected in siliconized tubes,^m and in tubes containing lithium heparin^m and potassium oxalate/sodium fluoride, respectively. Total protein concentration was measured, using refractometry.ⁿ Blood lactate concentration was measured immediately at collection.^o Packed cell volume was determined, using the microhematocrit method.^p Plasma, urine, and fluid osmolality were determined by use of freezing-point depression.^q Measurement of serum, plasma, and urine concentrations of Na, K, and Cl was made, using ion-specific electrodes.^r Fractional excretion of electrolytes was calculated as described.²³

Hyperosmotic fluid preparation—The 2,400 mosm/kg solution was made by aseptically transferring 1 L of stock

^e Cardiomax-II, Columbus Instruments Corp, Columbus, Ohio.

^f Cardiomax/IBM Interface, Cointbus Instruments Corp, Columbus, Ohio.

^g Marcaine HCl 0.75%, Winthrop-Breon Laboratories, New York, NY.

^h Quik-Cath, Travenol Laboratories, Deerfield, Ill.

ⁱ Medicut cannula, Argyle Corp, St Louis, Mo.

^j SF FL large lumen, CR Bard Inc, Bellerica, Mass.

^k Horse Thermodilution Catheter, Columbus Instruments Corp, Columbus, Ohio.

^l Model 79D, Polygraph, Data Recording System, Grass Medical Co, Quincy, Mass.

^m Vacutainer Systems, Becton, Dickinson & Co, Rutherford, NJ.

ⁿ TS meter, American Optical Corp, Keene, NH.

^o Model 23L Lactate analyzer, Yellow Springs Instrument Co Inc, Yellow Springs, Ohio.

^p Autocrit II, Becton, Dickinson & Co Inc, Parsippany, NJ.

^q Advanced Digimatic Osmometer, Advanced Instruments, Needham Heights, Mass.

^r Electrolyte 4 Analyzer, Beckman Instruments Inc, Brea, Calif.

NaCl^s solution (26.1% NaCl^s in distilled deionized sterile water) into 3 L of 0.9% NaCl.^t

Endotoxin infusion—*Escherichia coli* endotoxin^a was diluted (50 µg/ml) in lactated Ringer solution.^u The IV infusion^v of endotoxin was begun at time 0, at a rate of 100 ml/h for all horses. All endotoxin used was from the same manufacturer's lot.

Experimental protocol—A 2-period crossover design²⁴ was used to obviate the possible effects of repeated endotoxin challenge exposure. The sequence of the trials was randomly selected between horses (see Results). Horses were challenge exposed the second time after an interval of no less than 10 days (see Results). One complete data set was collected before endotoxin administration to establish baseline values for each horse and for each trial. When mean pulmonary arterial pressure increased by 10 mm of Hg, endotoxin infusion was stopped. Subsequently, cardiovascular data were collected, then either a 2,400-mosm/kg (hypertonic saline trial) or a 300-mosm/kg NaCl (isotonic saline trial) solution was administered IV at a dose of 5 ml/kg at a rate of 80 ml/min.^w Complete data sets were collected at 0.5-hour intervals for 4.5 hours after initiation of the endotoxin infusion. Data sets that did not include blood constituent measurements were collected at 0.25 and 0.75 hours. Blood constituent measurements alone were measured at 0.5 hour. Urine samples were collected as they were produced, and the number of episodes of micturition recorded. Urine volume was not quantified.

Statistical analysis—Repeated measures over time were obtained. Significance was set at $P < 0.05$. Analyses included the Wilcoxon signed-rank test and Student paired *t* test at each time interval to determine whether changes occurred between trials. A Pearson correlation was used to evaluate changes within trials. Confidence intervals were calculated to determine whether changes occurred from baseline values within trials. The same calculations were used to determine whether differences could be attributed to repeated endotoxin exposure.

Results

Unless otherwise noted, all references to time are in relation to the initiation of endotoxin infusion (0 hour).

Sequence of and period between trials—For the first and second trials, 2 and 3 horses respectively, were given hypertonic saline solution. Isotonic saline solution was administered during the other trial. The mean interval between endotoxin challenge-exposure periods was 12.8 ± 0.72 days. The minimal period between exposures was 10 days.

Endotoxin infusion—Endotoxin infusion was stopped as pulmonary arterial pressure increased by 10 mm of Hg from the baseline value. The quantity of endotoxin in-

^s Sodium chloride; Sigma grade, Sigma Chemical Co, St Louis, Mo.

^t 0.9% Sodium chloride irrigation, USP, Abbott Laboratories, North Chicago, Ill.

^u Lactated Ringer Injection, USP, Travenol Laboratories, Deerfield, Ill.

^v Ivac 630 volumetric infusion pump, Ivac Inc, San Diego, Calif.

^w Masterflex infusion pump, Barnant Co, Barrington, Mass.

fused ranged from 0.4 to 1 mg/horse or 0.96 to 2.5 µg/kg. The mean total endotoxin dose for all trials was 0.68 ± 0.09 mg/horse, or 1.64 ± 0.22 µg/kg. The mean infusion time was 0.135 ± 0.038 hours (8.1 ± 2.3 minutes). The time required for endotoxin infusion and subsequent sample collection prior to saline infusion was approximately 0.25 hour in all instances. There was no significant difference in the quantity of endotoxin infused between trials, or between the first and second endotoxin administrations.

Clinical data—Body weight was not significantly different between trials. All horses had signs of mild abdominal discomfort and became anorectic within 5 minutes after initiation of the endotoxin infusion. In all horses, signs of abdominal discomfort subsided by 0.75 hour (approx 0.6 hour after endotoxin infusion had been stopped). All horses sporadically produced unformed feces throughout the remainder of the trial. Horses recovered completely and unremarkably from the protocol and did not require further supportive care. Other data collected and indices are seen in Table 1.

CARDIOVASCULAR MEASUREMENTS

Pulmonary arterial pressure—The endotoxin infusion was stopped as pulmonary arterial pressure increased by 10 mm of Hg; however, by 0.25 hour, the mean pressure in horses of both groups had increased above that value (Fig 1a). At 0.75 hour, (at the end of fluid administration) the pulmonary arterial pressure during the isotonic saline trial was greater than that during the hypertonic saline trial. Pressure was relatively similar between trials throughout the remainder of the experimental protocol.

Cardiac output—After endotoxin administration (0.25 hour) cardiac output decreased during both trials (Fig 1b). At 0.75 hour, cardiac output during the hypertonic saline trial was similar to the baseline mean value and greater than that for the isotonic saline trial during which, the mean cardiac output was less than the respective baseline mean value. At almost all measurement periods throughout the remainder of the protocol, cardiac output during the hypertonic saline trial remained higher than that measured during the isotonic saline trial.

Heart rate—Heart rate did not increase after endotoxin administration (0.25 hour) during either trial. After fluids

Table 1—Data collected or indices calculated from horses infused with endotoxin and subsequently administered hypertonic or isotonic saline solution IV

	Trial	
	Hypertonic saline solution	Isotonic saline solution
Number of urinations	3 ± 0.28	0.8 ± 0.44
Urine osmolality (mosm/kg)	348.6 ± 28.45	601.2 ± 137.9
Fractional excretion (%)		
Na	14.08 ± 9.39	0.012 ± 0.008
K	78.05 ± 19.94	33.59 ± 8.6
Cl	18.9 ± 12.28	0.23 ± 0.061
Return of appetite (h)	1.5 ± 0.19	3.75 ± 0.32

All values are expressed as mean ± SEM and are significantly ($P < 0.05$) different between trials.

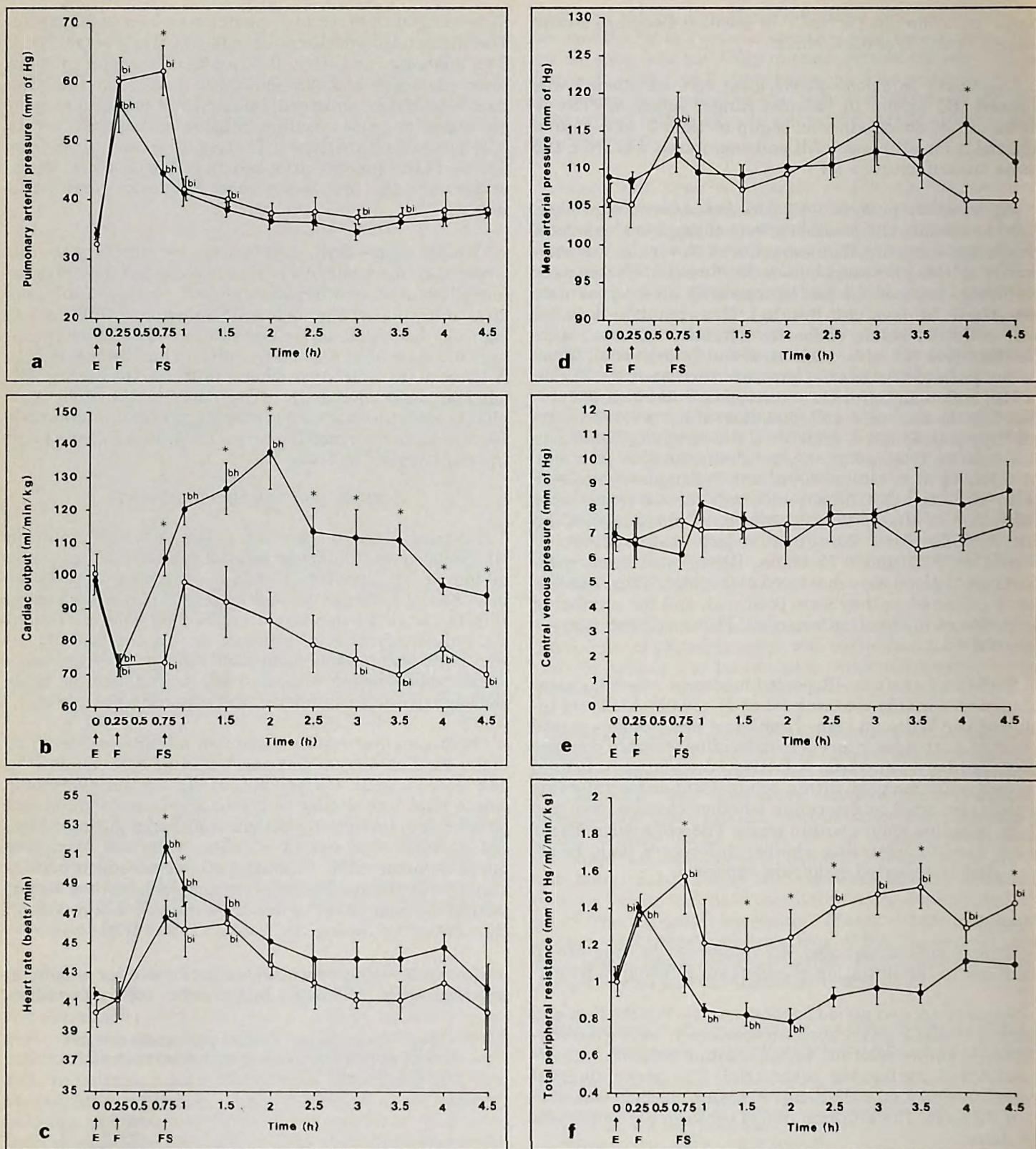


Figure 1—Mean (\pm SEM) repeated measures over time of cardiovascular variables during endotoxin infusion and subsequent iv administration of hypertonic (2,400 mosm/kg [●]) and isotonic (300 mosm/kg [○])NaCl solution to horses. E = initiation of endotoxin infusion; F = termination of endotoxin and initiation of NaCl administration; FS = termination of NaCl administration; bh = mean values different from baseline data for the isotonic saline trial, * = mean values different between groups.

a—Pulmonary arterial blood pressure

b—Cardiac output

c—Heart rate

d—Mean arterial pressure

e—Central venous pressure

f—Total peripheral resistance

had been administered (0.75, 1, and 1.5 hours), the measured heart rate values were greater than the respective baseline mean values during both trials (Fig 1c). Heart rate measurements during the hypertonic saline trial were greater than values obtained during the isotonic saline trial at 0.75 and 1 hours. Mean heart rates were similar between trials, compared with baseline values from 2 hours to the termination of the protocol.

Mean arterial pressure—Mean arterial pressure measured during the isotonic saline trial was greater after fluid administration (0.75 hour) than the respective baseline value (Fig 1d). At 4 hours, mean arterial pressure during the hypertonic saline trial was greater than that measured during the isotonic saline trial. There was no other between- or within-trial difference for the remainder of the protocol.

Central venous pressure—There was no within- or between-trial difference in central venous pressure throughout either trial (Fig 1e).

Total peripheral vascular resistance—After endotoxin infusion, total peripheral vascular resistance increased similarly during both trials (Fig 1f). After hypertonic saline administration (0.75 hour), vascular resistance decreased and remained at or below baseline values for the remainder of the protocol. After isotonic saline administration, there was an increase in vascular resistance (0.75 hour). During much of the remainder of the isotonic saline trial, total peripheral resistance was greater than that for the hypertonic saline trial and, later, was greater than the respective baseline mean value.

Pulmonary arterial blood temperature—At 1 hour after initiation of endotoxin infusion, blood temperature increased above baseline values and remained increased during both trials (Fig 2). At 3 hours, blood temperature measured during the isotonic increased above values measured during the hypertonic saline trial and remained increased for the duration of the trial.

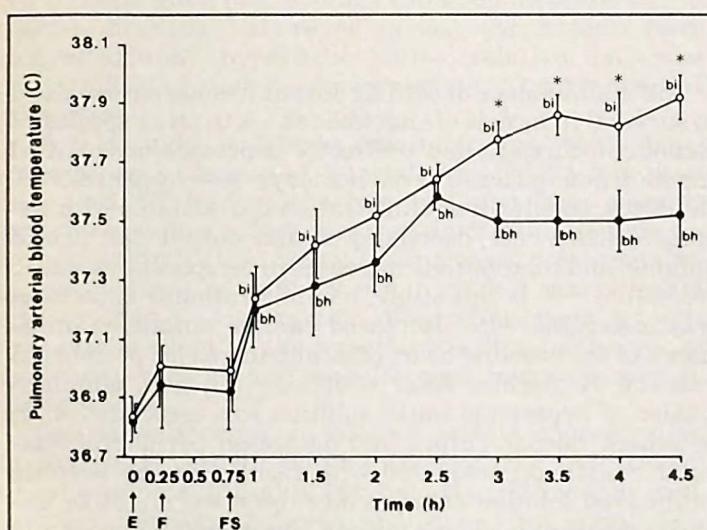


Figure 2—Mean (\pm SEM) repeated measures over time of mean pulmonary arterial temperature during endotoxin infusion and subsequent iv administration of hypertonic (●) and isotonic (○) NaCl solution. See Figure 1 for key.

Blood constituent measurements—From 1 hour through the remainder of the hypertonic saline trial, plasma osmolality (Fig 3a) Na (Fig 3b), and Cl (Fig 3c) concentrations increased, compared with the respective baseline values and compared with most of the similarly timed samples collected during the isotonic saline trial. Plasma K concentration (Fig 3d) decreased at 1 hour after initiation of the trial during both trials, but returned to the baseline mean value for the remainder of the respective protocols.

Blood lactate concentration (Fig 3e) increased during both saline infusion trials at 1 hour after initiation of the trial. Blood lactate measurements obtained during the hypertonic saline trial were decreased and returned to baseline values sooner (3 hours), compared with values for the isotonic saline trial (4 hours).

Plasma total protein concentration (Fig 3f) remained near the baseline value throughout the isotonic saline trial. At 0.5 hour, total plasma protein concentration decreased during the hypertonic saline trial, compared with the baseline value and with mean values obtained during the isotonic saline trial for periods 0.5, 1, 1.5, and 2 hours.

Packed cell volume (Fig 3g) was increased at 0.5 hour during the isotonic saline trial, compared with the respective baseline and with the mean PCV values obtained during the hypertonic saline trial. The high mean PCV value associated with isotonic saline administration persisted for the remainder of the protocol. Compared with the respective baseline value, mean PCV for the hypertonic saline trial tended to decrease ($P=0.092$) at 0.5 hour, but increased to greater than the baseline value at 3.5 hours. Mean PCV values associated with hypertonic saline administration were less than those associated with the isotonic saline trial at 3.5, 4, and 4.5 hours.

Discussion

In this study, a target pulmonary arterial pressure increase (10 mm of Hg) was used for endotoxin dose titration. Increases in pulmonary arterial pressure are measured early when endotoxin is delivered via the jugular vein.²⁵ Presumably, in this study, the rapid pulmonary response and cessation of endotoxin infusion decreased more serious sequelae to the horses and conserved the experimental protocol. Pulmonary arterial pressure measurements can be obtained easily, accumulated continuously, and evaluated rapidly. Therefore, pulmonary arterial pressure changes appear to be a reasonable signal for infusion endpoint. As can be seen in data obtained after endotoxin infusion, but before fluid administration, certain cardiovascular variables changed consistently within and between trials (0.25 hour, Fig 1). The homogeneity of responses should be considered in light of the range of total dose per horse and the dose per kilogram of body weight (0.4 to 1 mg/horse or 0.96 to 2.5 μ g/kg). Speculatively, if the infusion rate were slowed or fine tuned to body weight, lean body weight, or surface area, an even greater homogeneity of responses may have been evident. Possibly, the overshoot increase of pulmonary arterial pressure (0.25 hour, Fig 1) would have been avoided. Consideration of the long-term stability of responses in these experimental models should be questioned as well. Such questions may be answered if other dose-to-effect models are developed and evaluated.

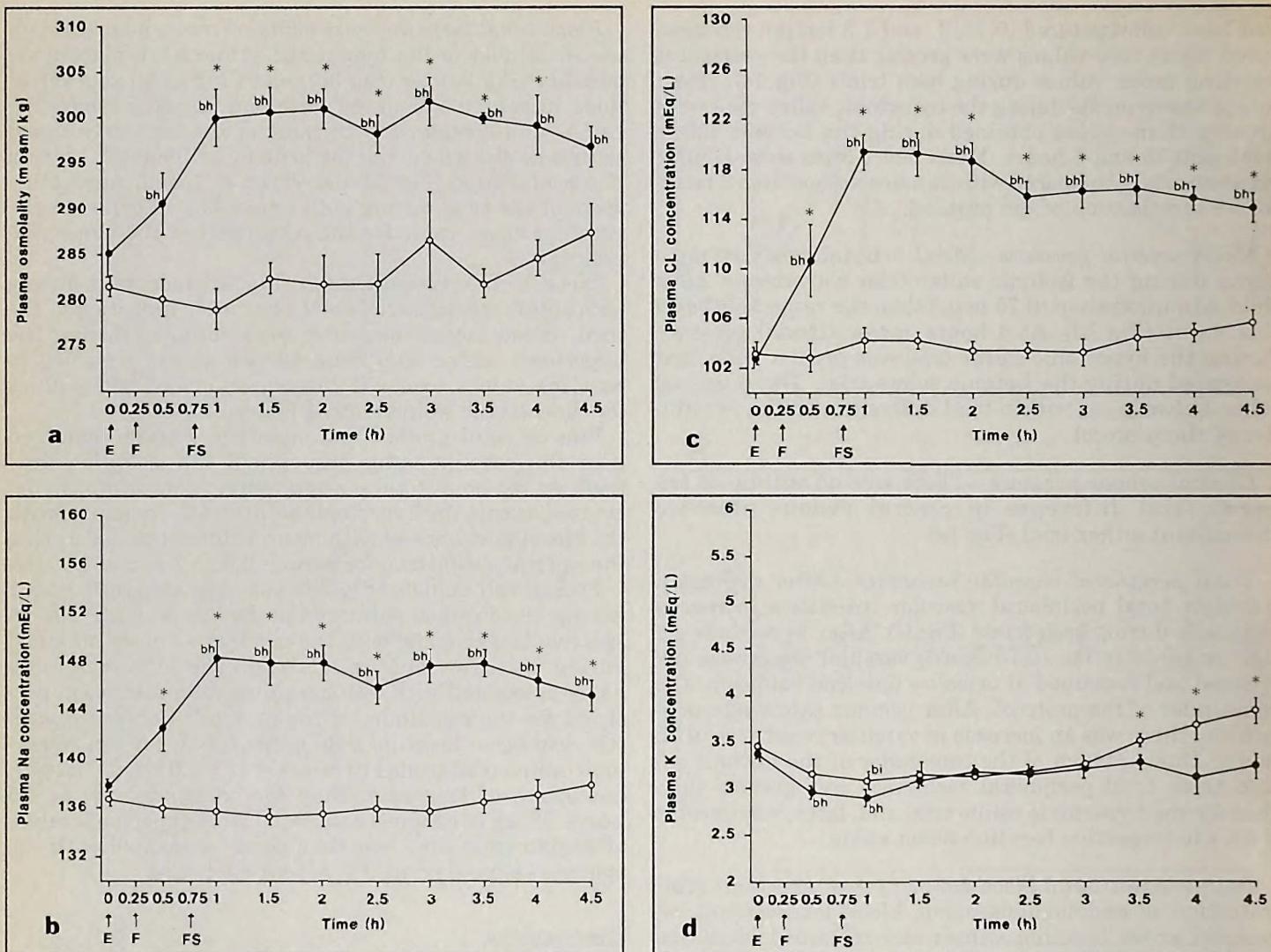
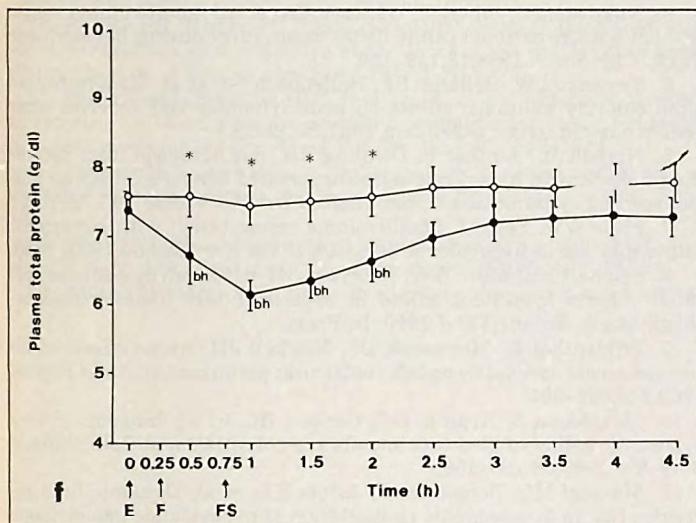
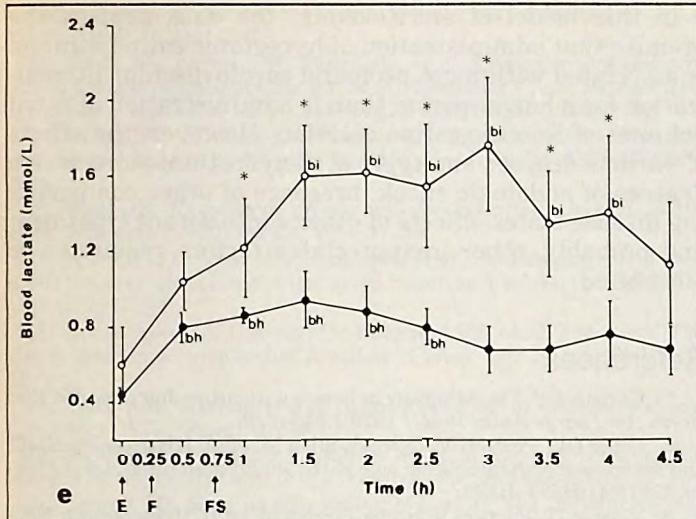


Figure 3—Mean (\pm SEM) reported measures over time of blood constituents during endotoxin infusion and subsequent IV administration of hypertonic (●) and isotonic (○) NaCl solutions. See Figure 1 for key.

- a—Plasma osmolality
- b—Plasma Na concentration
- c—Plasma Cl concentration
- d—Plasma K concentration

Pulmonary arterial pressure decreased more rapidly during the hypertonic saline trial than during the isotonic saline trial. Administration of hypertonic vs isotonic saline solution averted pulmonary arterial hypertension and increased pulmonary vascular resistance in models of hemorrhagic shock in dogs and horses,^{6,8} but not endotoxic shock in dogs.¹⁶ The relative increase in cardiac output during the hypertonic saline trial (Fig 1; 0.75 hour) may have been associated with greater distention and recruitment of the pulmonary vasculature and decreased pulmonary vascular resistance.²⁶ However, this would not explain the return to near baseline measurements of pulmonary arterial pressure evident during both trials for the remainder of the protocol. Pulmonary arterial pressure changes associated with cardiac output, or with the type of fluid administered were observed early. Later, either the pulmonary effects of endotoxin subsided, or long-term pulmonary vascular compensation for cardiac output developed irrespective of the fluids administered.

The maintenance of cardiac output has been correlated to survival in models of endotoxic shock in other species.²⁷ Endotoxin directly and indirectly depresses myocardial function and induces altered hemodynamic responses.^{28,29} In horses, endotoxin administration is associated with increased heart rate, decreased cardiac output and stroke volume, and concomitant increases in peripheral vascular resistance.^{25,30} In this study, administration of endotoxin was associated with decreased cardiac output, maintenance of the baseline heart rate, and increased peripheral vascular resistance. After endotoxin infusion, administration of hypertonic saline solution was associated with increased cardiac output and decreased peripheral vascular resistance, compared with results for the isotonic saline trial. Similar changes have been seen in other experiments designed to evaluate the effect of hypertonic solutions on hemorrhagic shock.^{2,3,5,8,14} Heart rate changes did not correlate to changes in cardiac output. Therefore, changes in cardiac output were associated with changes



in afterload, preload, or myocardial contractility.²⁷ Evidence from an in vitro study would suggest that increased Na concentration may actually diminish myocardial contractile function.³¹ However, in vivo experiments have suggested that hypertonic saline solution increases contractility.^{7,8} Such responses remain to be documented in horses.

In this study, endotoxin administration was not associated with decreased arterial pressure as has been described.^{32,33} In fact, the sole deviation from baseline arterial pressure values occurred during the isotonic saline trial (Fig 1d; 0.75 hour). The increased pressure mimicked changes evident in other models of sublethal endotoxemia.³⁴ Conservation of baseline mean arterial pressure, evident in the hypertonic saline trial, may be associated with altered vascular capacitance, as seen in other studies.^{2,3,5,11,14}

The early decrease in plasma protein concentration during the hypertonic saline trial may indicate increased plasma volume. Initially, PCV tended to decrease as well, but the difference between groups was not significant. The decrease in PCV was detected when total protein concentration was decreased and may be a further indication of volume shifts from the intracellular space as described.^{4,11,12,35} Discounting protein shifts that may take

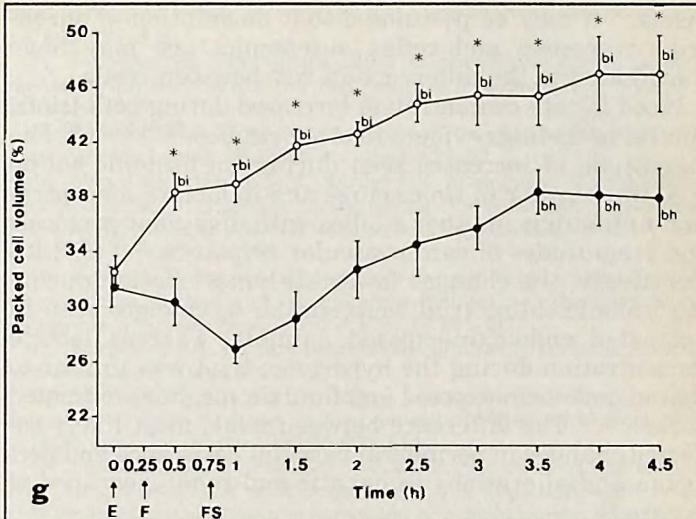


Figure 3—Mean (\pm SEM) reported measures over time of blood constituents during endotoxin infusion and subsequent iv administration of hypertonic (●) and isotonic (○) NaCl solutions. See Figure 1 for key. (Continued).
 e—Blood lactate concentration
 f—Total plasma protein
 g—PCV

place during endotoxemia and administration of hypertonic fluid, total protein concentration decrease would imply a 20% (approx 6 L) increase in plasma volume³⁶ at 1 hour. This volume change would be greater than that seen by some,^{4,11,35} but would compare with observations by others.^{8,12} To make this assumption is naive, especially when considering the complexity of plasma protein dynamics during endotoxemia and the theoretical possibilities associated with the administration of hypertonic saline solution.¹¹ It should be kept in mind that increases in vascular volume are apparently not necessary for the beneficial effects associated with hypertonic fluids.^{3,35}

In both trials, PCV increased above baseline values. Horses given isotonic saline solution had consistently increased PCV, which agreed with findings of other studies of equine endotoxemia.^{25,32,37} Late during the hypertonic saline trial, the increase in PCV was attenuated, compared with PCV values in response to isotonic saline administration. This response may have been attributable to RBC dilution by increased plasma volume. However, total plasma protein concentration was not decreased during this period. In light of data supporting a reflex arc involving the autonomic nervous system in response to hypertonic saline solutions,^{2,13,15} and the great capacity of horses to alter RBC numbers via autonomic mecha-

nisms,³⁸ it may be postulated that modulation of adrenergic responses and reflex autonomic tone may have contributed to the difference in PCV between trials.

Blood lactate concentration increased during both trials, similar to findings evident in other studies.^{32,34,37,39,40} The magnitude of increases seen during the isotonic saline trial was similar in time course and in lactate concentration to findings in other studies with divergent protocols and magnitudes of cardiovascular responses.^{32,37,39,40} Interestingly, the changes in lactate concentration during the isotonic saline trial were similar to changes seen in untreated endotoxin-exposed animals, whereas lactate concentration during the hypertonic trial was similar to that in endotoxin-exposed and flunixin meglumine-treated horses.^{39,40} The difference between trials most likely reflected changes in peripheral vascular resistance and perfusion and alterations in hepatic and renal clearance of lactate.⁴¹

As expected, pulmonary arterial blood temperature increased, as does rectal temperature, in response to endotoxin administration.³⁷ However, late in the protocol, blood temperature decreased during hypertonic, compared with isotonic, saline administration. The decrease in temperature may reflect increased perfusion of skin and cool muscle⁴² associated with the decrease in peripheral vascular resistance. However, late in the hypertonic saline trial, vascular resistance and cardiac output returned to near baseline values, which indicated attenuation of hypertonic fluid responses. During hemorrhagic shock, administration of hypertonic saline solution has been associated with shunting of blood away from muscle and skin to visceral organs.¹⁵ The relative blood temperature decrease late in the study may have been indicative of perfusion of cool skeletal muscle and skin and tapering of the shunt response to hypertonic saline solution.

Increases in plasma Na and Cl concentrations and osmolality were expected in response to administration of hypertonic saline solution. Urine output was not measured in horses of this study, but increased fractional excretion of Na, Cl, and K, decreased osmolality, and increased frequency of urination was identified during the hypertonic saline trial. Hypertonic saline and saline/dextran solutions have been associated with doubling of urine output when equal volumes of isotonic lactated Ringer or saline solution have been administered.^{6,8,43,44} This response may be associated with increased Na load, inhibition of vasopressin release and/or increased release of natriuretic factor associated with hypertonic saline administration.^{45,46}

Administration of hypertonic saline solution is associated with transient hypokalemia and kaliuresis in some, but not all, species.^{43,47} Decrease in plasma K concentration was seen early in the hypertonic saline trial. However, this does not explain decreased plasma K concentration during the isotonic saline trial. Decreased plasma K concentration during trials may have been attributable to dilution of plasma K concentration from IV administration of fluids or a response to endotoxin in this model.

It is important to note that during the hypertonic saline trial, horses' appetite returned sooner than it did during the isotonic saline trial. It can only be speculated that improved attitude and appetite were associated with improvements in cardiovascular and metabolic function.⁴⁸

In this model of endotoxemia, the data support the premise that administration of hypertonic saline solution is associated with more profound cardiovascular normalization for a longer period than is administration of equal volumes of isotonic saline solution. However, the effects of various degrees and types of dehydration, more severe degrees of endotoxic shock, presence of other compounding disease states, effects of other concomitant treatment and probably, other unappreciated factors remain to be elucidated.

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