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Neuroendocrine Responses to Hypertonic
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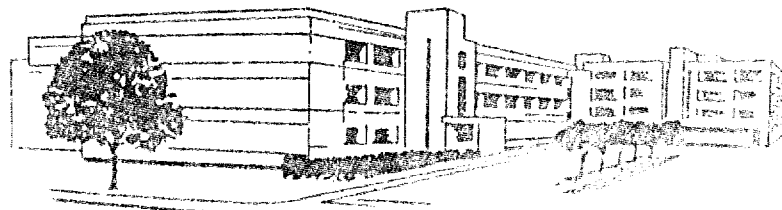
C.E. Wade,
J.P. Hannon, J.A. Loveday
R.I. Coppes Jr.
and
V.L. Gildengorin

Division of Military Trauma Research

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ABSTRACT

The neuroendocrine responses to resuscitation with 7.5% hypertonic saline/6% Dextran-70 (HSD) following hemorrhagic hypotension were evaluated in conscious swine. Following hemorrhage animals received 4 ml/kg of HSD (n=6) or 0.9% saline (n=8). Administration of normal saline did not alter cardiovascular function nor attenuate an increase in hormones. HSD rapidly improved cardiovascular function and acutely decreased ACTH, PRA, cortisol, norepinephrine (NE), epinephrine (E), aldosterone and lysine vasopressin levels (LVP). The initial decrease in ACTH, cortisol and aldosterone levels was due primarily to hemodilution associated with the expansion of plasma volume. The reductions in NE, E, LVP and PRA were greater than those attributed to hemodilution alone. Values for LVP, NE and E remained at values below those at the end of hemorrhage, but greater than basal levels, while PRA returned to values similar to these at the end of hemorrhage. The decrease in LVP, NE, and E following HSD resuscitation for the treatment of hemorrhagic hypotension may result from and contribute to the rectification of cardiovascular and metabolic function.



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NEUROENDOCRINE RESPONSES TO HYPERTONIC SALINE/ DEXTRAN RESUSCITATION FOLLOWING HEMORRHAGE

INTRODUCTION

Recently, hypertonic saline/dextran (HSD) has been shown to be an effective resuscitation solution for the treatment of hemorrhagic hypotension (1-3). The administration of this solution following hemorrhage results in improved cardiovascular function and decreased tissue oxygen demand (4-9). The net result is an increase in survival of animals following treatment with HSD (7-10). The role of neural and hormonal systems in the cardiovascular and metabolic responses to HSD is not clear. Following correction of hypovolemia with hypertonic saline (HS) alone, plasma hormone concentrations are decreased or unchanged from post hemorrhage values (11-13). Correction with HSD results in hormone levels being reduced to a degree similar to those obtained after administering an equal volume of normal saline (4). Two factors, hemodilution and either a decrease in secretion or an increase in clearance may play a role in reducing plasma hormone levels. Decreases in pressor hormones after HSD administration have been suggested as a mechanism in reducing total peripheral resistance (4) resulting in an improvement of cardiac output, while the fall in tissue oxygen demand has been associated with the reduction in plasma catecholamines (6). In the study reported here, we investigated the neuroendocrine responses to both hemorrhage and subsequent administration of HSD or an equal volume of normal saline in conscious pigs. This study was a component of a more extensive investigation comparing the resuscitative efficacy of HSD and its components (6,7). Specifically, in the current study we were concerned with the reason for changes in circulatory hormone concentrations following HSD administration and the possible actions of changes in these hormones to improve survival.

METHODS

Fourteen immature (25.2 ± 0.5 kg) Yorkshire pigs obtained from a commercial breeder (J.G. Boswell, Corcoran, CA) were studied. While anesthetized, the animals were splenectomized and chronically-instrumented with arterial and venous catheters seven to ten days before experimentation; the surgical procedures are described in detail elsewhere (6,7). Prior to the experiment, the animals were trained to rest quietly in a Pavlov sling and to accept a respiratory mask. On the day of the experiment, after an overnight fast, they were transported to the laboratory, placed in the sling, and fitted with a respiratory mask. After connecting the catheters to pressure transducers and the mask to a metabolic measuring unit, the animals were allowed to rest until a stable oxygen consumption was obtained; the rest period required 30 to 60 min. A thirty minute control period was then begun with an arterial blood sample (30 ml) drawn at its conclusion. Immediately thereafter, a fixed-volume hemorrhage was initiated (37.5 ml/kg/60 min). Over a 60 min period blood was removed progressively on an exponential scale so that successive 7.5 ml/kg increments were withdrawn at 9, 19, 31.5, 44, and 60 min. At each of these time points, the last 30 ml of blood removed was used for measurements; the control sample was included in the first increment. Immediately at the end of hemorrhage, either a bolus injection of 7.5% NaCl/6% Dextran-70 at 4 ml/kg ($n=6$) or an equal volume of normal saline ($n=8$) was given over one minute via the pulmonary artery catheter. Upon completion of the hemorrhage animals were randomly assigned to either treatment. Blood samples (30 ml) were collected at 5, 15, 30, 60, 120, 180, and 240 min after the completion of the hemorrhage.

Three aliquots from each blood sample were immediately placed, as appropriate, into chilled test tubes containing heparin, EDTA, or EDTA and sodium metabisulfide. The tubes were then placed in ice

water, and at the end of the experiment plasma was separated with a refrigerated centrifuge. Plasma was removed, allocated into individual tubes for each assay, and immediately frozen. For each hormone, all of the samples for a pig were measured within the same assay. Cortisol and aldosterone were measured using radioimmunoassay (RIA) kits from Diagnostic Products (Los Angeles, CA). The within-assay coefficients of variability and sensitivities were 3% and 0.2 ng/dl for cortisol and 8% and 1 ng/dl for aldosterone. The ACTH RIA assay (Nichols Laboratories, San Juan Capistrano, CA) had a within-assay coefficient of variability of 10% and a sensitivity of 11 pg/ml. Plasma renin activity (PRA) was measured by RIA for angiotensin I (New England Nuclear, Boston, MA) with a within-assay coefficient of variability of 7% and a sensitivity of ngAI/ml/hr. Plasma lysine vasopressin was measured using a method described previously (14). Assay sensitivity was 0.3 pg/ml and the within-assay coefficient of variability was 10%. Plasma catecholamines were measured by electrochemical detection (Bioanalytical Systems, West Lafayette, IN) after separation by HPLC (15). The within-assay variabilities were 5% and 3% for norepinephrine and epinephrine, respectively, and the sensitivities 5 pg/ml for both.

Data were evaluated with one way analyses of variance adjusted for repeated measures (16). Significance of the differences between means was determined by a Newman-Keuls test. Of the eight animals treated with normal saline, only values at 5 min post treatment are provided as all animals died shortly after the completion of hemorrhage (6,7). Of the six pigs entered into the study and treated with HSD, four survived the complete experimental period and two died, one at 70 min and the other at 190 min into the post-hemorrhage recovery period. For this reason, statistical analysis was limited to the first 60 min of recovery when all animals were living. The values in the text are means $\pm$ SEM. A probability of ≤ 0.05 was accepted as significant.

RESULTS

In response to hemorrhage, mean arterial pressure was progressively reduced from control values by 57 ± 11 mmHg at the end of hemorrhage, while cardiac index was decreased by 80 ± 20 ml/min/kg in animals to be treated with HSD (Table 1). Heart rate was increased from the control value by 49 ± 16 beats/min. Sixty minutes after the administration of the HSD solution, mean arterial pressure remained low and not significantly different from the value at the end of hemorrhage. Cardiac index was increased, and heart rate was not altered compared to values at the end of hemorrhage.

All hormone concentrations showed a progressive increase in response to hemorrhage (Fig. 1 and 2). At the end of hemorrhage, peak plasma levels were observed for all hormones except ACTH, which attained peak levels at 31.5 min into the hemorrhage.

Plasma renin activity (PRA) was reduced significantly following treatment with HSD, but this reduction did not persist beyond 15 min post-treatment (Fig. 1). Plasma aldosterone concentration fell significantly over the first 15 min after treatment and remained relatively constant, significantly lower than the value seen at the end of hemorrhage but still significantly greater than the control level (Fig. 1).

Plasma ACTH levels were progressively reduced after treatment and were not significantly different from time control values at 60 min into the recovery period (Fig. 1). Changes in cortisol concentration did not follow changes in plasma ACTH (Fig. 1). Cortisol values were acutely decreased immediately after treatment, but within 60 min returned to levels similar to those recorded at the end of hemorrhage.

Lysine vasopressin (LVP) levels were sharply reduced by 58% immediately after treatment (Fig. 2). Thereafter, LVP values showed a further gradual decrease, but remained significantly elevated compared to control values. Plasma levels of both epinephrine and norepinephrine also showed significant, acute

reductions immediately after treatment (Fig. 2). The epinephrine decrement persisted throughout the recovery period, but the values were significantly greater than those recorded during the control period. Norepinephrine levels, while acutely decreased after treatment, increased progressively over the remainder of the recovery period, but were still significantly lower than the values recorded immediately after hemorrhage.

The injection of HSD resulted in the movement of fluid into the vascular compartment. This expansion of plasma volume caused hematocrit values to decrease from 22 ± 0.8 to $18 \pm 0.6\%$ within 5 min after treatment. This level was maintained over the remainder of the recovery period. The hematocrit decrement was due to a calculated (17) increase in plasma volume on the order of $32.6 \pm 2.4\%$ which in turn produced a dilution of circulating hormones. Table II summarizes the predicted hormone concentrations that would be attributable to dilution alone. The observed (measured) levels for cortisol, ACTH, and aldosterone approximate those that would be predicted from dilution alone. The concentrations of LVP, PRA, epinephrine, and norepinephrine were decreased beyond levels which could be attributed to hemodilution alone.

Administration of an equal volume of normal saline following hemorrhage did not alter mean arterial pressure, cardiac output or heart rate (Table III). Plasma hormone concentrations were not decreased 5 min following normal saline infusion (Table III). Further, increases in norepinephrine, cortisol and aldosterone were observed following normal saline administration.

DISCUSSION

The administration of hypertonic saline/dextran (HSD) increases survival following hemorrhagic hypotension (7-10). The increase in survival is attributed to the ability of HSD to expand plasma volume (4,7-9), improve venous return and consequently cardiac output (4-9), as well as reduce tissue oxygen demand (6). Hemorrhagic hypotension is associated with increases in plasma hormone concentrations which are rectified following fluid resuscitation. In the present study, the decrease in plasma levels of vasopressin, PRA and catecholamines observed following HSD resuscitation may contribute to these putative mechanisms of action by altering capillary permeability, blood flow distribution or metabolism. Shackford and coworkers (11) infused hypotensive swine with a hypertonic sodium lactate solution or Ringer's lactate to correct central venous pressure. Immediately following resuscitation, plasma levels of vasopressin, ANF and renin achieved basal values with both treatments even though a smaller volume of hypertonic solution was administered as compared to the volume of Ringer's lactate. In a study of patients undergoing cardiopulmonary bypass, Cross and colleagues (12,13) post-operatively administered 1.8% hypertonic saline or normal saline to maintain blood pressure and pulmonary capillary wedge pressure. The volume of fluid required to attain these end points was less in patients receiving hypertonic saline. The post-operative increases in ACTH, cortisol, aldosterone and angiotensin II were attenuated in patients receiving hypertonic saline, while the increase in vasopressin was not changed. In response to a constant volume of HSD (200 ml) administered to hemorrhagic hypotensive sheep, Kramer et al. (4) found the decreases in vasopressin, norepinephrine and epinephrine similar to those following an equal volume of normal saline. Basal hormone levels were attained within 30 min following resuscitation. In contrast, the present study of swine showed no decrease in plasma hormone levels in animals administered an equal volume of normal saline while a rapid decrease in hormone levels was noted following HSD. However, the hormone levels attained following HSD were still increased as compared to basal values.

The endocrine response to hemorrhage is characterized by increases in all vasoactive hormones, increases that would rectify the decrease in effective blood volume by changing the capacitance of both arterial and venous systems as well as altering capillary pressures (19-23). In response to treatment with HSD, all of the primary vasoactive hormones (epinephrine, norepinephrine, vasopressin and the renin-angiotensin system) were acutely decreased. This reduction was associated with an acute increase in cardiac index and mean arterial pressure, presumably because of an increase in blood volume and a decrease in total peripheral resistance (4,5,7).

The increase in vasoactive hormones following hemorrhage acts synergistically to induce selective vasoconstriction and redistribution of blood flow to maintain blood pressure and cardiac output (19-23). Though vasoactive hormones are acutely reduced following treatment with HSD, possibly contributing to the increase in venous return, and thus cardiac index, the plasma concentrations are still greatly elevated. The nadirs of these hormones post treatment with HSD were still well above circulating levels shown to elicit maximum effects on the cardiovascular system (21,24). Therefore, the decreases in vasoactive hormones following HSD may not contribute to the maintenance of cardiovascular function during recovery even with further changes in plasma levels.

The reduction in plasma hormone concentrations after treatment with HSD could be achieved by one or more of the following factors: hemodilution, an increase in clearance, or a decrease in release. As noted in Table II, the initial decreases in the levels of cortisol, aldosterone, and ACTH are predominately due to hemodilution resulting from the mobilization of fluid into the vascular space following HSD infusion (4,6). Decreases in vasopressin, PRA, norepinephrine and epinephrine, however, were only partially due to hemodilution as the reductions exceeded those estimated to be attributable to hemodilution alone (Table 3).

Vasopressin, norepinephrine and epinephrine are cleared by both the liver and kidneys. During

hemorrhagic hypotension renal and hepatic blood flow are reduced, thus reducing the clearance of hormones (18). Immediately following resuscitation with HSD blood flow to the liver and kidneys is increased (18), possibly facilitating the clearance of vasopressin, epinephrine and norepinephrine.

Release of the hormones may also be attenuated by changes due to administration of HSD. The primary stimulus for the release of vasopressin, PRA and catecholamines during hemorrhage is the decrease in blood pressure/vascular volume sensed by baroreceptors (19-22). Immediately after injecting HSD, blood pressure is increased and plasma volume expanded. Though transient in the present study, the increase in blood pressure may attenuate the stimulus for the release of these hormones. Further, via the low pressure baroreceptors, the sustained increase in plasma volume may attenuate hormone release as well.

Changes in the release of hormones in response to reductions in blood pressure and volume are usually closely coupled. However, while initially showing an acute decrease beyond that due to hemodilution, PRA increased following the fall in blood pressure after treatment. Though the levels of vasopressin, norepinephrine, and epinephrine partially regressed over the next hour of the recovery period, renin-angiotensin levels rose, as indicated by an increase in PRA, attaining values after 60 min of recovery that were not significantly different from the end of hemorrhage. The dissociation of PRA from the changes in vasopressin and catecholamines following HSD suggest factors other than changes in pressure or volume may be involved. The results of other studies in which fluid resuscitation was given to establish a fixed pressure support this idea. While there were no differences in systemic and pulmonary hemodynamic measurements, in the studies of Cross et al. (12,13) the responses of angiotensin II, ACTH, and aldosterone were attenuated in patients receiving hypertonic fluid as compared to those administered normal saline, thereby suggesting an increased sensitivity of hormonal regulation to baroreceptor input. However, the response of vasopressin was not altered. In contrast, Kramer et al. (4) found no difference in norepinephrine, epinephrine

or vasopressin concentrations when comparing HSD to an equal volume of normal saline even though HSD resulted in significant increases in mean arterial and central venous pressures, indicating a decreased sensitivity of hormonal regulation to baroreceptor input. These findings and those of the present study suggest that factors other than blood pressure/vascular volume are modulating the release of hormones.

Administration of HSD after hemorrhage causes a decrease of about 33% in tissue oxygen demand (6). In part, a reduction in hormone levels following resuscitation with HSD may be responsible for this decrease since the hormones measured in the present study are known to have wide-ranging metabolic actions. While some actions such as the catabolic effects of cortisol are long acting (23), of concern are the rapid responses to HSD leading to an immediate decrease in tissue oxygen demand. For example, the actions of the catecholamines (epinephrine and norepinephrine) on metabolism are well documented (20,25,26). After treatment with HSD there was a pronounced decrease in pH accompanying the reduction in plasma catecholamine levels (6). Such a decrease in pH is an expected consequence of improved circulation through previously ischemic tissue. In the presence of acidosis, the increase in oxygen uptake due to catecholamines is attenuated (25,26). Though the catecholamine concentrations are still increased compared to control values following HSD resuscitation, the concomitant decrease in pH may attenuate their influence on oxygen consumption (6). The net effect of the reduction of both catecholamines and pH following hypertonic saline/dextran may be the reduction of tissue oxygen demand (6).

Flux of fluids between various compartments in the body and rectification of total body fluid balance may be modulated by various hormones (27,28). The reduction of vasopressors, such as the plasma catecholamines, may contribute to the maintenance of blood volume after treatment since they could reduce the driving pressure (arterial capillary pressure) moving fluid out of the vascular space. However, only an acute increase in blood pressure was noted following HSD. The continued increase in plasma cortisol

following resuscitation may provide a driving force for the movement of fluids from the intracellular compartment to the interstitial space by increasing extracellular osmolality (27). In the absence of fluid resuscitation, an increase in cortisol is essential to the restitution of blood volume after hemorrhage (23,27). In addition, catecholamines, vasopressin and cortisol may have a direct action on capillary permeability by antagonizing inflammatory mediators known to increase permeability (28). Therefore, continued elevation of plasma hormones above basal levels following HSD may contribute to the redistribution of fluid between body compartments, alter blood flow distribution, and decrease tissue oxygen demand thereby facilitating recovery from hemorrhage.

The hormonal responses to hypertonic saline or HSD have been suggested as essential for the beneficial effects of the solutions. Unfortunately, specific roles of the reduction in plasma hormone concentrations following HSD administration for treatment of hemorrhagic hypotension are not clear. Specific studies should be directed at vasopressin and catecholamines in that factors other than hemodilution are contributing to their decrease.

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Table I

Hemodynamic Parameters in response to hemorrhage and subsequent treatment with HSD.

Time (min)	MAP (mmHg)	CI (ml/min/kg)	HR (b/min)
<u>Control</u>			
0	104 ± 4	178 ± 16	120 ± 6
<u>Hemorrhage</u>			
60	52 ± 9*	98 ± 14*	169 ± 21*
<u>Treatment</u>			
65	84 ± 4+*	202 ± 19+	148 ± 13+
75	67 ± 5*	175 ± 17+	142 ± 9+
90	61 ± 5*	163 ± 16+	140 ± 9+
120	62 ± 8*	137 ± 25+*	163 ± 15*
180	69 ± 7*	137 ± 20+*	158 ± 16*
240	72 ± 11*	137 ± 19+*	164 ± 14*
300	74 ± 7*	165 ± 24+	168 ± 11*

+ Significantly different from the 60 min value at the end of hemorrhage

* Significantly different from control values

Table II

Comparison of hormone levels predicted due to hemodilution with those observed 5 minutes following HSD administration.

	Predicted	Observed
Cortisol ($\mu\text{g/dl}$)	18.7 ± 2.5	15.4 ± 2.2
ACTH (pg/ml)	580 ± 127	304 ± 42
Aldosterone (ng/dl)	32.9 ± 7.1	17.9 ± 2.7
PRA (ngAl/ml/hr)	16.6 ± 3.7	$9.3 \pm 2.1^*$
Epinephrine (pg/ml)	13032 ± 3488	$1595 \pm 723^*$
Norepinephrine (pg/ml)	7161 ± 2332	$2473 \pm 1017^*$
Vasopression (pg/ml)	698 ± 62	$257 \pm 38^*$

* Significantly different from predicted values,
 $P < 0.05$

Table III

Hemodynamic and plasma hormone values ($\bar{x}$ SEM) observed in animals (n=8) treated with normal saline.

	Control	Hemorrhage	5 min Resuscitation
MAP (mmHg)	105 $\pm$ 6	55 $\pm$ 3*	56 $\pm$ 5*
CI (ml/min/kg)	150 $\pm$ 8	91 $\pm$ 13*	104 $\pm$ 13*
HR (b/min)	113 $\pm$ 3	204 $\pm$ 20*	214 $\pm$ 17*
Epinephrine (pg/ml)	137 $\pm$ 32	22262 $\pm$ 2826*	23960 $\pm$ 3598*
Norepinephrine (pg/ml)	202 $\pm$ 41	17790 $\pm$ 2607*	25682 $\pm$ 5170*+
Lysine Vasopression (pg/ml)	9 $\pm$ 1	994 $\pm$ 237*	1349 $\pm$ 621*
ACTH (pg/ml)	123 $\pm$ 34	764 $\pm$ 104*	711 $\pm$ 122*
Cortisol (μ g/dl)	3.3 $\pm$ 0.8	19.8 $\pm$ 4.1*	27.8 $\pm$ 6.1*+
Aldosterone (ng/dl)	2.0 $\pm$ 0.3	43.1 $\pm$ 6.7*	54.0 $\pm$ 8.9*+
PRA (ngAI/ml/hr)	0.8 $\pm$ 0.2	11.7 $\pm$ 1.3*	12.6 $\pm$ 2.8*

* Significantly different from control

+ Significantly different from hemorrhage

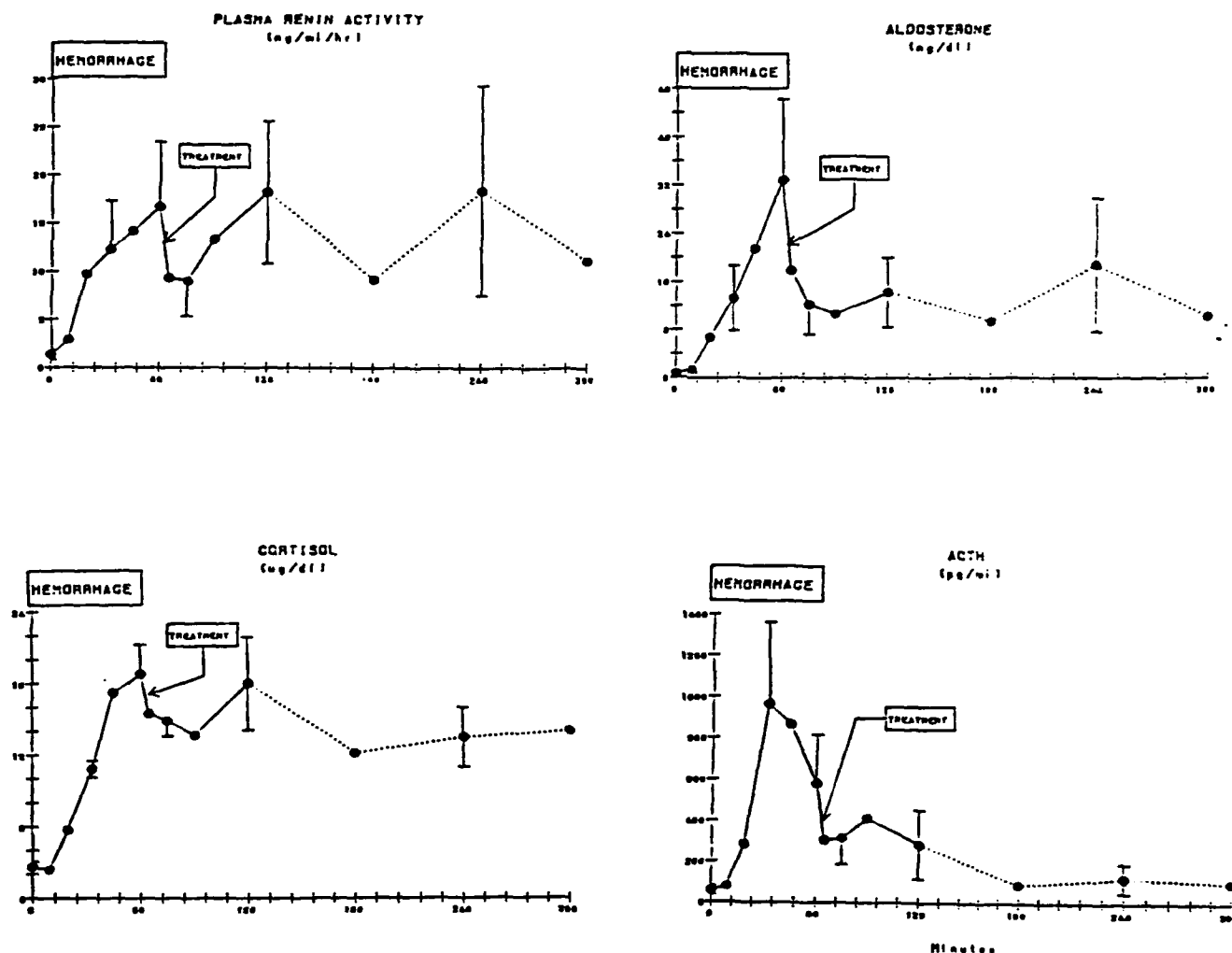


Figure 1: Plasma concentrations ($\bar{X}$ SEM) of PRA, aldosterone, cortisol and ACTH in conscious swine (n=6) hemorrhaged and subsequently treated with HSD. Dotted lines indicate animals lost to follow up. One animal died at 70 minutes and another at 190 minutes.

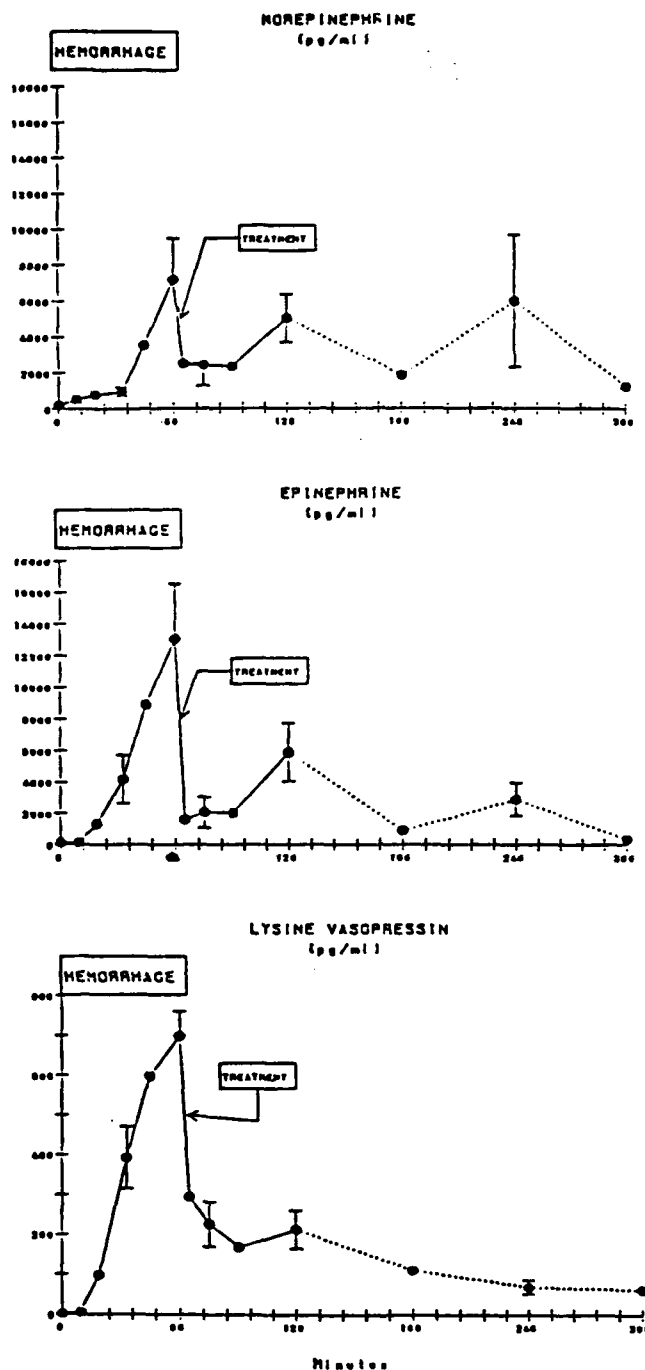


Figure 2: Plasma levels of $\bar{X}$ SEM of norepinephrine, epinephrine, and lysine vasopressin in conscious swine (n=6) hemorrhaged and subsequently resuscitated with HSD. Dotted lines indicate animals lost to follow up (See Figure 1.)

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