

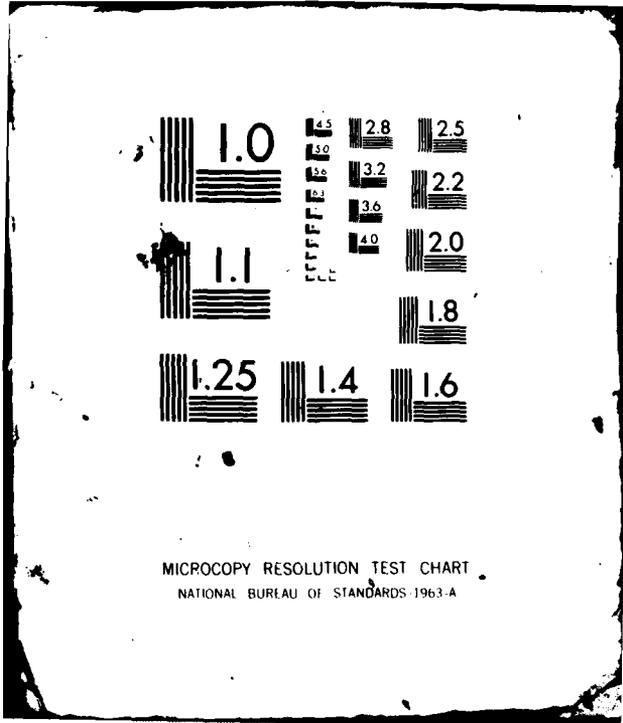
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PHYSIOLOGIC ASPECTS OF PORCINE HEMORRHAGE. V. ARTERIAL METABOLI--ETC(U)  
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PHYSIOLOGIC ASPECTS OF PORCINE HEMORRHAGE

V. Arterial Metabolite, Electrolyte, and Enzyme Alterations during Spontaneous Recovery from 30 and 50 percent Blood Volume Loss in the Conscious Animal

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DIVISION OF RESEARCH SUPPORT

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Institute Report No. 115  
--Hannon and Skala

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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER LAIR Institute Report No. 115	2. GOVT ACCESSION NO. AD A112753	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Physiologic Aspects of Porcine Hemorrhage. V. Arterial Metabolite, Electrolyte, and Enzyme Alterations During Spontaneous Recovery from 30 and 50 Percent Blood Volume Loss in the Conscious		5. TYPE OF REPORT & PERIOD COVERED Interim, Aug-Dec 81 Animal
7. AUTHOR(s) John P. Hannon, PhD, and James H. Skala, PhD		8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS Divs of Combat Casualty Care & Research Support Letterman Army Institute of Research Presidio of San Francisco, CA 94129		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS Project 3M161102BS10 Task BA; WU 256
11. CONTROLLING OFFICE NAME AND ADDRESS US Army Medical Research & Development Command Fort Detrick, Frederick, MD 21701		12. REPORT DATE February 1982
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		13. NUMBER OF PAGES 37
		15. SECURITY CLASS. (of this report) UNCLASSIFIED
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report)  This document has been approved for public release and sale; its distribution is unlimited.		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number)  Hemorrhage; Hypotension; Arterial Metabolite; Electrolytes; Enzymes; Swine		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number)  see reverse		

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20. Abstract

A porcine animal model, designed to simulate physiologic characteristics of the combat casualty, was used to assess the effects of moderate and severe blood loss on the metabolite, electrolyte, and enzyme concentrations of arterial blood in the absence of anesthesia or other interventions. Young domestic swine, six animals per group, were subjected to 30 and 50 percent hemorrhage of their estimated blood volume for a one-hour period while in a conscious recumbent state. Before hemorrhage and for five hours after, metabolite, electrolyte, and enzyme concentrations were measured in arterial plasma. Six additional pigs, treated similarly except for hemorrhage, served as controls. Transient hyperglycemia, lactacidemia, creatininemia, hypokalemia, and magnesium increments were observed after 50 percent blood loss. At the point of maximum change, plasma glucose had increased from 4.84 to 9.40 mmoles/l, lactic acid from 1.13 to 11.36 mmoles/l, creatinine from 78.8 to 119.5 umoles/l, magnesium from 1.15 to 1.56 mEq/l, while plasma potassium had decreased from 4.5 to 3.7 mEq/l. Plasma urea concentrations in these animals increased progressively, from 2.64 to 4.79 mmoles/l, during the spontaneous recovery period. Pigs subjected to 30 percent blood loss showed similar changes in the plasma concentrations of glucose and lactate, but significantly less than those observed after 50 percent hemorrhage. The plasma concentrations of sodium, chloride, calcium, and phosphate were unaffected by hemorrhage, while both 30 and 50 percent blood loss led to significant decrements in the plasma concentrations of alanine transaminase, lactic dehydrogenase, creatine kinase, and alkaline phosphatase. Significant posthemorrhage negative correlations were found between mean arterial pressure and the plasma concentrations of glucose, lactate, creatinine, and magnesium. Significant posthemorrhage negative correlations were observed also between plasma bicarbonate and plasma glucose, lactate, and creatinine. Posthemorrhage glucose concentration was positively correlated with lactate and magnesium concentrations and negatively correlated with potassium concentration, while lactate concentration was positively correlated with creatinine and magnesium concentration. Posthemorrhage hyperglycemia was concluded to be the result of increased epinephrine secretion and hepatic glycogenolysis, lactacidemia to elevated muscle glycolysis, and hypokalemia to intracellular accumulation of potassium by the skeletal musculature. Speculatively, transient creatininemia following hemorrhage was attributable to reduced renal clearance and progressive uremia to increased protein catabolism and increased hepatic urea synthesis.

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ABSTRACT

A porcine animal model, designed to simulate physiologic characteristics of the combat casualty, was used to assess the effects of moderate and severe blood loss on the metabolite, electrolyte, and enzyme concentrations of arterial blood in the absence of anesthesia or other interventions. Young domestic swine, six animals per group, were subjected to 30 and 50 percent hemorrhage of their estimated blood volume for a one-hour period while in a conscious recumbent state. Before hemorrhage and for five hours after, metabolite, electrolyte, and enzyme concentrations were measured in arterial plasma. Six additional pigs, treated similarly except for hemorrhage, served as controls. Transient hyperglycemia, lactacidemia, creatininemia, hypokalemia, and magnesium increments were observed after 50 percent blood loss. At the point of maximum change, plasma glucose had increased from 4.84 to 9.40 mmoles/l, lactic acid from 1.13 to 11.36 mmoles/l, creatinine from 78.8 to 119.5 umoles/l, magnesium from 1.15 to 1.56 mEq/l, while plasma potassium had decreased from 4.5 to 3.7 mEq/l. Plasma urea concentrations in these animals increased progressively, from 2.64 to 4.79 mmoles/l, during the spontaneous recovery period. Pigs subjected to 30 percent blood loss showed similar changes in the plasma concentrations of glucose and lactate, but significantly less than those observed after 50 percent hemorrhage. The plasma concentrations of sodium, chloride, calcium, and phosphate were unaffected by hemorrhage, while both 30 and 50 percent blood loss led to significant decrements in the plasma concentrations of alanine transaminase, lactic dehydrogenase, creatine kinase, and alkaline phosphatase. Significant posthemorrhage negative correlations were found between mean arterial pressure and the plasma concentrations of glucose, lactate, creatinine, and magnesium. Significant posthemorrhage negative correlations were observed also between plasma bicarbonate and plasma glucose, lactate, and creatinine. Posthemorrhage glucose concentration was positively correlated with lactate and magnesium concentrations and negatively correlated with potassium concentration, while lactate concentration was positively correlated with creatinine and magnesium concentration. Posthemorrhage hyperglycemia was concluded to be the result of increased epinephrine secretion and hepatic glycogenolysis, lactacidemia to elevated muscle glycolysis, and hypokalemia to intracellular accumulation of potassium by the skeletal musculature. Speculatively, transient creatininemia following hemorrhage was attributable to reduced renal clearance and progressive uremia to increased protein catabolism and increased hepatic urea synthesis.



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## PREFACE

This is the fifth in a series of reports on the physiologic responses of domestic swine to hemorrhagic hypotension. Earlier reports were concerned with chronic catheterization techniques, hemodynamic responses, and acid-base changes of conscious animals subjected to moderate and severe blood loss.

We wish to express appreciation to LTC Paul B. Jennings, VC, and MAJ Robert S. Dixon, VC, for surgical preparation of the animals, and to Diane G. Arevalo for superb animal care during all stages of the study. We are also highly indebted to Mary F. Lyons for performing most of the chemical analyses reported here, Dr. Virginia Gildengorin for her invaluable assistance in statistical evaluation of the data, Sue Davis for the numerous hours she spent in typing, proofreading, and assembling the manuscript, and JoAnne Melody for the many editorial and format improvements incorporated in this report.

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PHYSIOLOGIC ASPECTS OF PORCINE HEMORRHAGE  
V. ARTERIAL METABOLITE, ELECTROLYTE, AND ENZYME ALTERATIONS DURING  
SPONTANEOUS RECOVERY FROM 30 AND 50 PERCENT BLOOD VOLUME LOSS IN THE  
CONSCIOUS ANIMAL

Extensive experimental work during and shortly after World War II provided the basis for most of our current knowledge on the metabolic effects of hemorrhage and shock. These investigations, which ranged from the subcellular to the organismic level, were conducted almost entirely using laboratory rats and mongrel dogs. The results have been reviewed by Engel (1,2), Wilhelmi (3), Wiggers (4), and Levenson, et al (5). In subsequent studies, laboratory rats and mongrel dogs have continued to serve as the predominant experimental animals. In recent years, however, the domestic pig has become increasingly popular as a large animal model for investigating the effects of hemorrhage and shock. This would appear attributable to the many anatomic and functional similarities displayed by swine and man (6,7), including their hemodynamic (8,9) and acid-base (10) responses to severe blood loss.

Up to the present time, the metabolic consequences of hemorrhage in swine has received limited attention. Severe blood loss and resultant shock in this species has been shown to lead to hyperglycemia (11-13) and lactic acidemia (11,14-18). It is also reported to cause an increase in anaerobic myocardial glucose catabolism (16), reduced skeletal muscle glucose phosphorylation (13), phosphatemia (13), hyperkalemia (17,19), and an increase in plasma acid hydrolase concentration (17,18,20). Associated effects have included increased adrenal secretion of epinephrine and cortisol (12), elevated epinephrine and norepinephrine levels in venous blood (12) and, variously, unaltered (12) or increased (13) blood insulin concentrations. Anesthetized pigs were used in most of these metabolic studies, a variable that seriously modifies the responses to severe blood loss (21). Only Stremple et al (16) and Carey and his coworkers (11,12,15) have used conscious animals. Most porcine studies, furthermore, were concerned with the immediate effects of hemorrhage and shock.

The present study was designed to provide additional information about the metabolic consequences of moderate and severe blood loss in the conscious domestic pig. Included were measurements of arterial glucose, lactate, creatinine, urea, all major electrolytes, and selected plasma enzymes. Attention was directed to alterations that occur both during and subsequent to blood loss.

## METHODS

Eighteen young domestic swine, both barrows and gilts, were used in this study. They were distributed into three groups, each containing six animals; one group served as a control, a second group was subjected to 30 percent hemorrhage, and the third group was subjected to 50 percent hemorrhage. We have previously reported details concerning the procurement, housing, surgical implantation of chronic aortic catheters, postsurgical treatment, hemorrhage procedures, and experimental conditions associated with data collection from these pigs (9,22).

Arterial blood samples were taken in heparinized (1000 units/ml) syringes, chilled to 4 C, and centrifuged for plasma collection. The samples were obtained at the same time points as the previously reported hemodynamic (9), and blood gas and acid-base (10) measurements. Briefly, baseline control values were obtained in duplicate or triplicate at 10-minute intervals subsequent to at least 30 minutes of unrestrained recumbent rest. Thereafter, the animals were hemorrhaged over a one-hour period to achieve 30 or 50 percent loss of the estimated blood volume or, in the case of the controls, remained unmolested for an equal time period. Subsequently, post-hemorrhage, or control, samples were taken at 0, 30, 60, 120, 180, 240, and 300 minutes of spontaneous recovery.

Plasma glucose, urea nitrogen, lactic dehydrogenase, creatine kinase, and alkaline phosphatase were assayed with a GEMSAEC centrifugal analyzer (Electronucleonics, Inc., Fairfield, NJ) with Spinchem<sup>®</sup> test kits marketed by SmithKline Instruments, Inc., Sunnyvale, CA. The GEMSAEC analyzer was used also to assay for creatinine with an Ultrachem<sup>™</sup> test kit marketed by Harleco, American Hospital Supply Corp., Gibbstown, NJ, and for alanine and aspartate transaminases, and lactic acid with Sigmasystem<sup>™</sup> test kits marketed by Sigma Chemical Co., St. Louis, MO. Technicon<sup>™</sup> autoanalyzer procedures (Technicon Instruments, Tarrytown, NY) were used for assays of plasma sodium and potassium (23), calcium and phosphate (24), and chloride (25). Magnesium was determined by the procedure of Gindler and Heth (26).

Data from all three groups were first evaluated with two factor (group x time) analyses of variance. Next, significant main effects and interactions were localized by two factor analyses of variance applied to the groups taken in pairs (control versus 30 percent hemorrhage, control versus 50 percent hemorrhage, and 30 versus 50 percent hemorrhage). Finally, significant within-group time effects were identified by single factor analyses of variance. In addition, Pearson Product-Moment correlation coefficients were computed for selected metabolite and electrolyte data obtained from hemorrhaged pigs after 30 minutes of spontaneous recovery.

## RESULTS

### Plasma Metabolites:

Hyperglycemia was observed immediately after loss of either 30 or 50 percent of the estimated blood volume (Figure 1). The effect was modest, but significant (Tables 1-3) for the pigs subjected to 30 percent hemorrhage, the values rising from a control level of  $4.74 \pm 0.168$  (mean  $\pm$  SEM) mmol/l to  $5.66 \pm 0.273$  mmol/l. As evidenced by a significant group  $\times$  time interaction (Table 2), a more pronounced hyperglycemia was observed in pigs subjected to 50 percent blood loss. The maximum effect in this group occurred 30 minutes posthemorrhage, at which point the values had increased from a control level of  $4.84 \pm 0.168$  to  $9.40 \pm 1.410$  mmol/l. During the subsequent course of spontaneous recovery, plasma glucose levels remained high in the 30 percent group but reverted somewhat in the 50 percent group. Even at the end of the recovery measurements, however, both hemorrhage groups displayed high plasma glucose levels, with the mean values being distinctly higher in the 50 percent group as compared to the 30 percent or control groups. The control nonhemorrhage group showed no significant time-related changes in plasma glucose concentration (Table 3).

Lactacidemia was also evident immediately after the hemorrhage episode (Figure 1, Table 1). Again, the effect was significantly more pronounced in the pigs subjected to 50 percent blood loss (Table 2). Accordingly, 30 percent hemorrhage was associated with a twofold increase in plasma lactate concentration, from  $1.13 \pm 0.097$  to  $2.11 \pm 0.300$  mmol/l, while 50 percent hemorrhage was associated with a tenfold increase, from  $1.13 \pm 0.112$  to  $11.36 \pm 1.802$  mmol/l. Over the course of the recovery period the values reverted toward, and ultimately were no different from, values recorded during the initial control period. The control group of pigs showed no significant time-related changes in plasma lactate concentration (Table 3).

Plasma urea concentrations (Figure 2) of control pigs decreased from an initial level of  $2.96 \pm 0.536$  at the start of the experimental period to  $2.54 \pm 0.332$  mmol/l at the end of the recovery period, a modest but significant time-related change (Table 3). Pigs subjected to 30 percent blood loss showed no significant changes as a function of time (Table 3) but, because of this, they showed a significant group  $\times$  time interaction (Table 2) when compared to control pigs. Fifty percent hemorrhage, in contrast to the forgoing, caused plasma urea concentration to increase progressively and significantly (Table 3) over the course of spontaneous recovery. The values thus rose from a control level of  $2.64 \pm 0.225$  to  $4.79 \pm 0.451$  mmol/l after 300 minutes of recovery. This change was significantly different from the changes, or lack thereof, recorded in control pigs and pigs subjected to 30 percent hemorrhage (Tables 1,2).

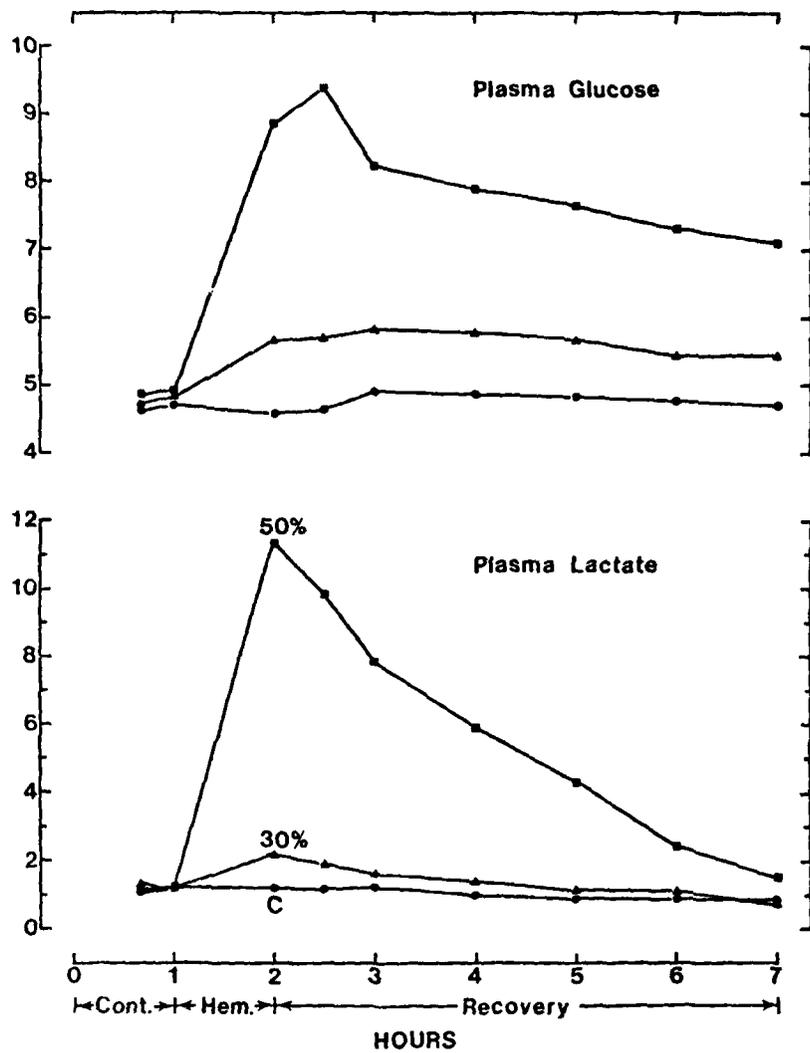


Figure 1. Effects of 30% and 50% blood loss on the concentrations of glucose and lactate of arterial plasma. C refers to control animals (N = 6 pigs per group). Ordinate values are expressed in mmol per liter.

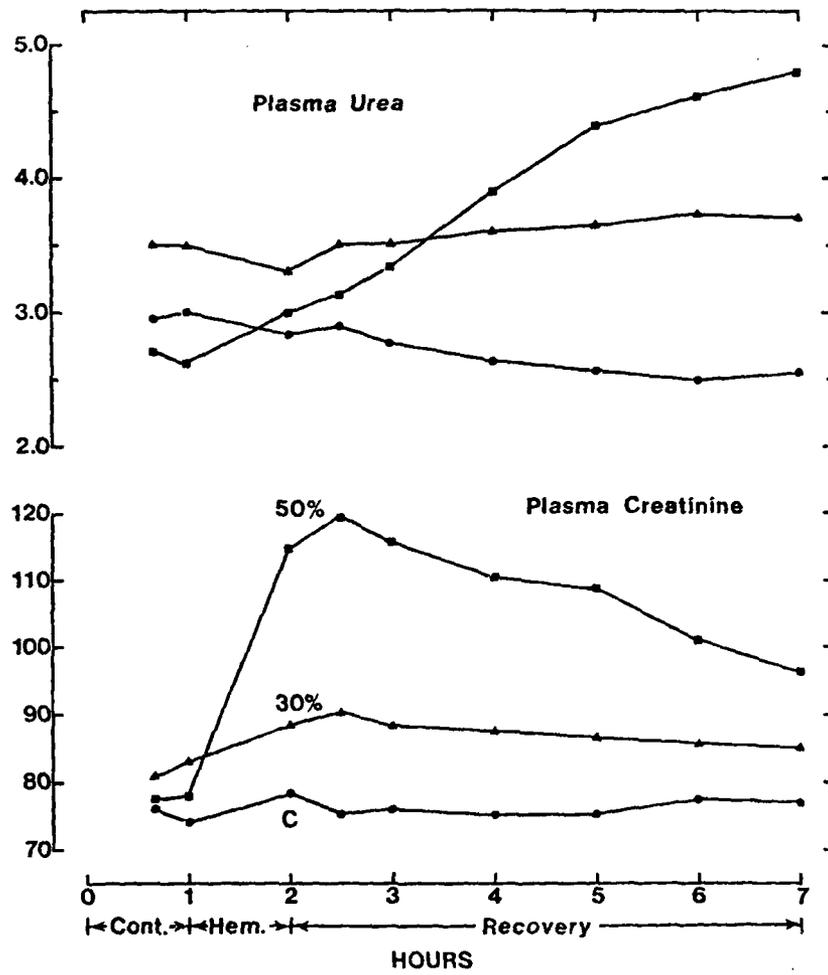


Figure 2. Effects of 30% and 50% blood loss on the concentrations of urea and creatinine of arterial plasma. C refers to control animals (N = 6 pigs per group). Ordinate values are expressed in mmol per liter for urea and  $\mu$ mol per liter for creatinine.

Plasma creatinine concentrations were not altered as a function of time in the control pigs, nor were they altered by 30 percent hemorrhage (Figure 2, Tables 2,3). Only 50 percent loss of the estimated blood volume led to statistically significant effects (Tables 1,3). The values in these animals rose from a control level of  $78.8 \pm 5.04 \mu\text{mole/l}$  to  $119.5 \pm 11.50 \mu\text{mole/l}$  at the 30-minute point of spontaneous recovery (Tables 1,3).

#### Plasma Electrolytes:

No significant changes in the plasma concentrations of calcium and chloride were observed either as a function of time in control pigs or as a function of time or blood loss in the hemorrhaged pigs. A similar lack of significant change was obtained in the measurements of plasma sodium and phosphate concentrations (Figure 3, Tables 1-3).

In contrast to the forgoing, plasma potassium showed a modest but significant (Table 3) decrease immediately after 50 percent loss of the estimated blood volume; the values were reduced from a control level of  $4.5 \pm 0.12$  to  $3.7 \pm 0.07 \text{ mEq/l}$ . Thereafter, the concentrations in this group of pigs reverted toward control levels over the course of spontaneous recovery. The reversion accounted for the significant group x time interactions contained in Tables 1 and 2. Plasma potassium values recorded in the control group did not change as a function of time, and the values in the 30 percent hemorrhage group did not change as a function of time or blood loss (Tables 1-3).

Plasma magnesium concentration showed a transient, modest, but significant, increase in pigs subjected to 50 percent blood loss (Figure 3, Table 3). The values rose from a prehemorrhage control level of  $1.15 \pm 0.058$  to  $1.56 \pm 0.173 \text{ mEq/l}$  after one hour of spontaneous recovery. Subsequently, the values reverted toward prehemorrhage control levels. No statistically significant time-related changes were recorded in the control or 30 percent hemorrhage groups when evaluated independently (Table 3). There was, however, a significant group x time interaction between these two groups (Table 2); the interaction was attributable to the combined tendency for progressively decreasing values over time in the control group and progressively increasing values over time in the 30 percent group.

#### Plasma Enzymes:

Decreased concentrations of several plasma enzymes were observed after hemorrhage (Table 4). This effect was more common in pigs subjected to 30 percent blood loss than in pigs subjected to 50 percent blood loss. Accordingly, the 30 percent group showed significantly decreased values for alanine transaminase, lactic dehydrogenase, creatine kinase, and alkaline phosphatase, while the 50 percent group showed decrements for only alanine transaminase and lactic

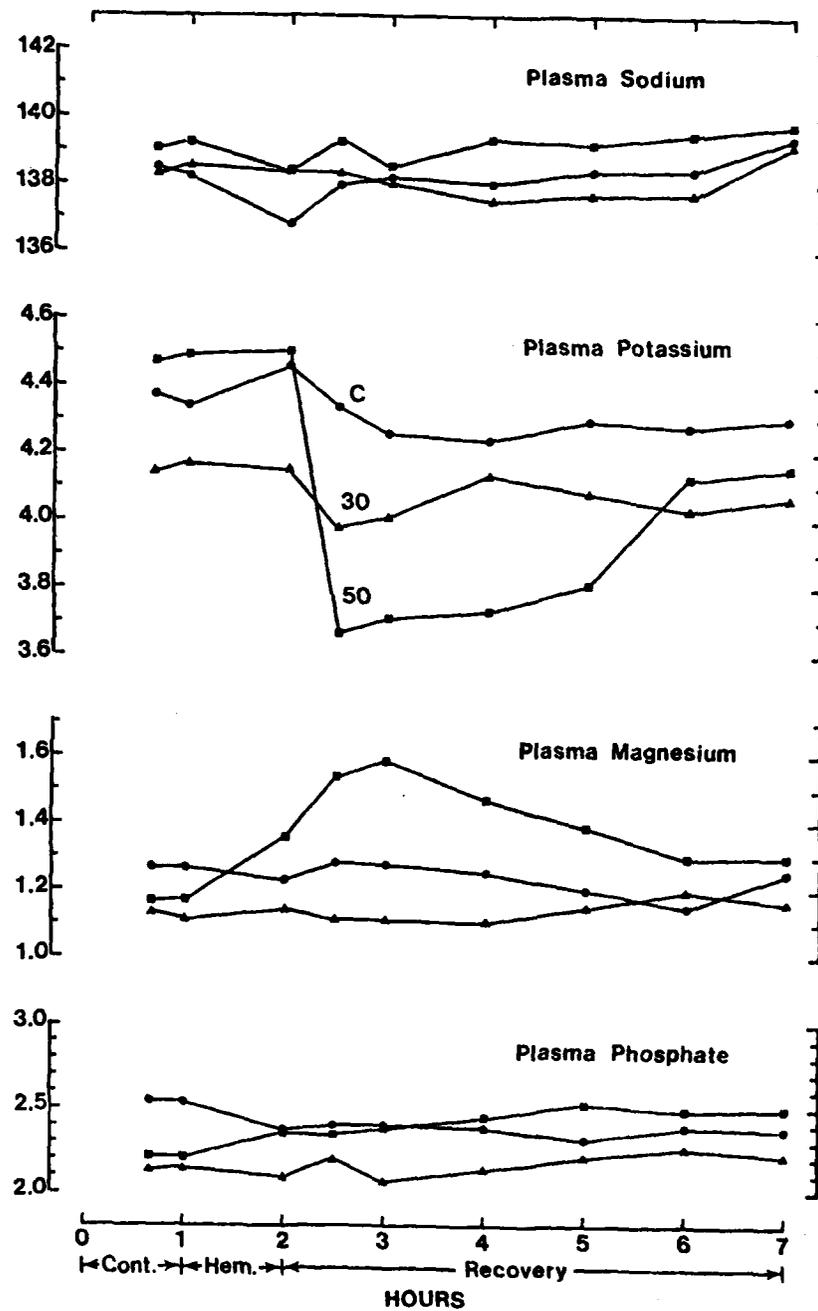


Figure 3. Effects of 30% and 50% blood volume loss on the arterial plasma concentration of sodium, potassium, magnesium, and phosphate. C refers to control animals. Six pigs were included in each group. Ordinate values in mmol per liter for phosphate and in mEq per liter for all other electrolytes.

dehydrogenase. The lack of significant change in creatine kinase and alkaline phosphatase in the 50 percent group was attributable to one animal that showed no change in the concentrations of these enzymes after hemorrhage and a second animal that showed increased concentrations; all the other pigs showed unaltered or decreased concentrations. Aspartate transaminase concentration showed no significant alterations attributable to either time or hemorrhage. One enzyme, lactic dehydrogenase, showed a diurnal increase in concentration that became apparent in the control group at the 60-minute point of the recovery period and in the 30 and 50 percent groups at the 300-minute point of the recovery period.

#### Functional Interrelationships:

A number of the experimental variables measured here showed peak or nadir values 30-60 minutes after hemorrhage (Figures 1-3). Similar effects were observed previously in these same pigs in measurements of hemodynamic (9) and acid-base (10) variables. Since this suggested the existence of functional interrelationships between variables, Pearson Product-Moment correlation coefficients were calculated for the 30-minute posthemorrhage values of mean arterial pressure, bicarbonate, glucose, lactate, creatinine, magnesium, and potassium. The results of these calculations are summarized in Table 5. A significant negative correlation was obtained between mean arterial pressure and the concentrations of bicarbonate, glucose, lactate, creatinine, and magnesium; i.e., the greater the pressure decrements the greater the concentration increments. Plasma bicarbonate concentration also was negatively correlated to the plasma concentrations of glucose, lactate, and creatinine. The only other significant negative correlation coefficient was between the concentrations of glucose and potassium. Significant positive correlation coefficients were obtained between glucose and lactate, glucose and magnesium, lactate and creatinine, and between lactate and magnesium.

#### DISCUSSION

##### Carbohydrate Metabolism:

The alterations in blood glucose observed in the present study are qualitatively consistent with those reported in earlier investigations of hemorrhagic hyperglycemia in swine. Quantitatively, however, the responses recorded here were distinctly different from those reported by others. In large measure, these differences would appear to be attributable to dissimilar experimental conditions. Here, 30 percent blood loss in the conscious animal led to a 19 percent increase and 50 percent blood loss led to a 94 percent increase in plasma glucose. In anesthetized pigs, Carey and Wallack (11) reported a 2.6 percent increase following 10 percent hemorrhage and a 175 percent increase

following a 60-minute episode of sustained hypotension at 60 torr. Wright and Henderson (13) also used anesthetized pigs to investigate glucose tolerance during sustained hypotension at an arterial pressure of 50 torr. Their data were reported in graphic form and comparison to the results reported here was complicated further by fatalities in a third of the animals. It would appear that the hyperglycemic response following 30 minutes of hypotension at 50 torr (before the glucose tolerance test) led to a blood glucose increment that did not exceed 100 mg/dl; i.e., about 5.5 mmole/l. This is in distinct contrast to the 9.4 mmole/l recorded at about the same time point and the same mean arterial pressure, in conscious pigs subjected to 50 percent blood loss. Insofar as we are aware, the only previous study of hemorrhagic hyperglycemia in conscious swine was reported by Carey, et al (12). They investigated the effects of slow and rapid blood loss (30 percent of the estimated blood volume) on blood glucose concentration, adrenal catecholamine and cortisol secretion, and serum insulin concentration. Rapid blood loss, over 30 minutes, led to a more marked hyperglycemia than slow (over 80 minutes) blood loss. Their graphic data would indicate an increment of about 25 percent in the former group and about 10 percent in the latter. These values would bracket those obtained after 30 percent hemorrhage in the present study. Carey et al (12) also investigated the blood glucose alterations that occurred subsequent to the initial hemorrhage episode and found further concentration increments. Again, a more pronounced response was obtained in the group that was bled rapidly. The posthemorrhage plasma glucose values in this group increased progressively over a 90-minute period, reaching concentrations nearly 100 percent over baseline; there was no tendency for glucose concentrations to revert toward baseline levels during the posthemorrhage period. Thus, the recovery characteristics in the study of Carey et al (12) were not only quantitatively but also qualitatively different from those observed in the present investigation. There would appear to be a ready explanation for these discrepancies, however. In the study of Carey et al (12), blood sampling for biochemical analyses during the posthemorrhagic period raised the total loss to 45 percent of the initial blood volume. Such additional losses probably elicited an additional hyperglycemic response; the progressive increases in adrenal epinephrine secretion and venous epinephrine concentration recorded during the posthemorrhagic period (12) would argue for this explanation.

The alterations in arterial lactate concentration recorded here also are consistent, at least qualitatively, with data obtained in other studies of hemorrhagic hypotension in swine. Again, much of the published information was obtained from anesthetized animals, and in most instances the Wiggers' procedure (27) was used to assess the effects of sustained hypotension followed by the reinfusion of shed blood. In such studies (14,15,17,18), plasma or serum lactate concentrations up to 8 times the control level were recorded during the hypotensive period. It would appear that conscious pigs were used in

only two studies of hemorrhagic lactacidemia. In one of these, Oringer and Carey (15) recorded a maximum, fourfold increase in serum lactate during a 90-minute period of sustained arterial hypotension at 55 torr. In the other study, Stremple et al (16) subjected conscious pigs to 40 percent blood loss, 4 hours after being anesthetized for catheterization. Their data, reported in graphic form, showed a sustained lactacidemia over a 40-minute posthemorrhagic period. The values, calculated as excess lactate, would seem to indicate a 40- to 50-fold increase after hemorrhage. These results are both qualitatively and quantitatively different from those observed here. Thus, lactacidemia in the present investigation was transient, and a maximum 10-fold increase in concentration was recorded in pigs losing 50 percent of their estimated blood volume. It is possible that carry-over effects of anesthesia or physical restraint during the study influenced the outcome of the results reported by Stremple et al (16).

Investigations in species other than swine have shown that hemorrhagic hypoglycemia is the result of compensations for reduced arterial pressure, while hemorrhagic lactacidemia is the result of inadequate tissue oxygen delivery and, as a consequence, anaerobic glycolysis (1-5). In the present study, such mechanisms are suggested by the negative correlations between mean arterial pressure and the plasma concentrations of lactate and glucose 30 minutes after the hemorrhage episode. Both of these metabolites show negative correlations with the degree of metabolic acidosis, as evidenced by reduced plasma bicarbonate concentration. Finally, a positive correlation between glucose concentration and lactate concentration suggests that increments in the former were contributing to increments in the latter.

The hyperglycemic response to hemorrhage was first described in 1877 by Claude Bernard (28) and Von Mering (29). The liver, because of its high glycogen content, was considered the likely source of the added glucose, and the first direct evidence supporting this view was obtained in 1894 by Schenck (30). He showed that hyperglycemia did not occur after hemorrhage if vascular supply to the liver was ligated. Thirty years later, the presumed decrease in hepatic glycogen was actually demonstrated in hemorrhaged rabbits by Tachi (31), and in the following year, similar evidence was obtained in guinea pigs by Aggazzotti (32). Subsequently, hepatic glycogenolysis has been seen in hemorrhaged rats (33,34). In addition, Robertson (35) and Beatty (36) showed in dogs that hemorrhage led to an increase in the glucose concentration of hepatic venous blood.

Almost all workers have attributed hemorrhagic hyperglycemia to an increase in adrenal epinephrine secretion. Elevated blood epinephrine levels in hypotensive animals were thus reported as early as 1916 by Bedford and Jackson (37), and actual increases in adrenomedullary epinephrine secretion have been observed consistently by later workers in a variety of species (38,39), including swine (12). Metabolic

acidosis associated with hemorrhagic hypotension potentiates the effect (40,41) and, in this respect, it is noteworthy that the degree of hyperglycemia observed in the present study was correlated significantly with the degree of bicarbonate reduction, an index of metabolic acidosis. A similar relationship was reported many years ago by Tatum (42).

Available evidence indicates that lactacidemia after hemorrhage is attributable to reduced peripheral blood flow, especially to skeletal musculature, with a consequent reduction in tissue oxygen delivery and an elevated rate of anaerobic glycolysis. Hemorrhagic hyperglycemia facilitates the increased rate of peripheral glucose utilization. Support for these concepts is found in the study of Russell, Long, and Engel (43), which showed that the fall in blood glucose concentration after evisceration was markedly enhanced by severe hemorrhage. Only an increased rate of peripheral, principally muscle, glucose utilization could account for such an effect. Beatty (36,44) subsequently reported increases in the femoral arteriovenous glucose and lactate differences which could not be attributed to diminished blood flow; after severe hemorrhage, the arteriovenous glucose difference increased 12-fold while blood flow decreased to only a fourth of control values. In addition to enhanced blood glucose catabolism, Tachi (31) showed that hemorrhage also led to accelerated muscle glycogenolysis.

#### Nitrogen Metabolism:

Insofar as we are aware, there has been only one study of nitrogen metabolism in swine subjected to hemorrhage. This study was reported in 1919 by Mary Buell (45), who investigated the daily excretion of nitrogen metabolites by two conscious sows (150 and 164 kg) before and after hemorrhages of 13 ml/kg (about 25 percent blood volume loss). In one of these pigs she also measured blood levels of total nitrogen and urea nitrogen two hours after the hemorrhage episode. Hemorrhage led to creatinuria, but little or no change in the excretion of creatinine, uric acid, urea, or total nitrogen. Blood changes after hemorrhage included an increase in urea concentration and a decrease in total nitrogen (presumably plasma protein) concentration. The results obtained in the present experiment are generally consistent with those reported by Buell, particularly when the 50 percent hemorrhage group is considered. After hemorrhage, these pigs showed a transient increase in plasma creatinine concentration, a delayed increase in plasma urea concentration, and a progressive reduction in plasma protein concentration (unpublished data).

In species other than swine, severe blood loss has been shown to cause numerous alterations in total body nitrogen metabolism. As early as 1915, Gyorgy and Zunz (46) observed aminoacidemia in dogs subjected to repeated hemorrhages, but not after a single modest hemorrhage. They concluded that hypotension was a prerequisite to the increase in blood amino acid concentration. Shortly after these results appeared,

nearly identical results were reported by Taylor and Lewis (47), who observed in addition that severe hemorrhage also led to an increase in the nonprotein nitrogen and urea concentrations of the blood. They attributed these effects to a release of amino acids stored in tissues or, alternatively, to hydrolysis of serum or tissue protein. Subsequent studies have consistently verified the latter alternative, not only after hemorrhage but also in various other forms of trauma and shock (1,4,5,48). Increased protein catabolism after severe blood loss appears to be localized primarily in the skeletal musculature. Thus, Russell et al (43) observed enhanced aminoacidemia in eviscerated rats after hemorrhage and, more directly, Kline (49) found a marked increase in the femoral arteriovenous amino acid difference of oligemic, intact dogs; the latter effect exceeded by far the probable change in femoral blood flow. Kline (49) also found an increase in the visceral arteriovenous amino acid difference, but felt that this was attributable to reduced blood flow. Reduced visceral blood flow, however, has been shown by Engel et al (50) and Seligman et al (51) to compromise hepatic amino acid clearance and so contribute to the degree of rise in blood amino acid concentration after hemorrhage. In the terminal stages of shock, increased protein breakdown probably occurs in most body tissues (5,48).

The increase in blood urea concentration after hemorrhage is attributable to the combined effects of increased hepatic synthesis and reduced renal clearance (1,4,48,51). In the present study, the progressive rise in urea concentration after 50 percent blood loss would suggest that reduced hepatic blood flow during the early stages of spontaneous recovery may have compromised hepatic urea synthesis, and it was only after adequate hepatic blood flow was reestablished that accumulated plasma amino acids could be cleared and the urea synthesized. Under such circumstances, uremia would not be expected during the early stages of recovery. An alternative explanation would be that plasma amino acid concentration and, consequently, hepatic urea synthesis increased progressively during the course of the recovery period. This seems unlikely in view of the recovered hemodynamic function displayed by the same pigs (9).

The factors responsible for the transient rise in plasma creatinine concentration observed in this study, particularly after 50 percent blood loss, are not readily apparent. Insofar as can be determined, such increases have not been previously reported for animals subjected solely to hemorrhagic hypotension. Beecher and his colleagues (52) reported increased blood creatinine levels in wounded soldiers during World War II, but in these casualties the hemorrhagic hypotension was accompanied by tissue trauma. Trauma, particularly to the skeletal musculature, has been shown to lead to increased blood creatinine levels, as might be anticipated (4,48). Generally, plasma creatinine concentration is determined by production rate, which is largely a reflection of muscle mass, and the excretion rate which is roughly proportional to glomerular filtration rate (53). If muscle

mass does not change rapidly, alterations in plasma creatinine are determined almost exclusively by changes in glomerular filtration rate; clinically, an increased plasma creatinine level almost always indicates depressed renal clearance (53). Thus, it would appear reasonable to conclude that the alterations seen during spontaneous recovery in the hemorrhaged pig are largely attributable to changes in renal blood flow and glomerular filtration rate. It is perhaps noteworthy in this regard that the increased plasma creatinine concentration 30 minutes after the hemorrhage episode was correlated negatively with arterial pressure. This would suggest that cardiac output and renal function were depressed at this same time point. Data to substantiate these speculations are obviously needed.

#### Plasma Electrolytes:

The plasma electrolyte alterations seen here were restricted for the most part with pigs subjected to 50 percent loss of the estimated blood volume, and in these animals the effects were limited to an increase in magnesium concentration and a decrease in potassium concentration. In both instances, the point of maximum change occurred during the early stages of spontaneous recovery. The concentrations of sodium, calcium, chloride, and phosphate were unaltered by hemorrhage or recovery therefrom. In an earlier report on these pigs (10), decrements in plasma bicarbonate concentration were described, and in the present report an increase in lactate concentration, which contributes to cation-anion balance, was recorded during hemorrhage and recovery. Finally, plasma protein, which acts as an anion, was decreased after hemorrhage (unpublished data). Overall electrolyte balance was not altered by hemorrhage. This is illustrated by the following tabulation of the mean cation and anion concentrations (in mEq/l) obtained before and 30 minutes after 50 percent blood loss.

	CATIONS		ANIONS	
	Before	After	Before	After
Sodium	138	139	Chloride	101
Potassium	4.5	3.8	Bicarbonate	31.0
Calcium	4.7	4.6	Phosphate*	4.0
Magnesium	2.3	3.2	Proteinate*	13.6
			Lactate	1.1
Total	149.5	150.6		150.1
				149.7

\*Phosphate concentration was calculated as  $1.8 \times \text{mmoles/l}$  and proteinate concentration was calculated from the Van Slyke equation (54).

In this tabulation, the impact of hemorrhage on anion--but not on cation--concentrations, is readily evident. Specifically, maintenance of cation-anion balance after hemorrhage entailed combined decrements in bicarbonate and proteinate concentrations that were nearly equal to the increment in lactate concentration.

In the literature, one finds little information on the electrolyte alterations of swine subjected to hemorrhage. We could locate only four articles, each containing measurements of a single electrolyte, and only one of these reports involved hemorrhage in conscious animals. This was the study of Stremple et al (16), which showed that loss of 40 percent of the blood volume led to a decrease in the potassium concentration of coronary sinus plasma. The magnitude of the decrease was comparable to that observed here after 50 percent blood loss. The other three studies involved sustained hemorrhagic hypotension induced in the anesthetized animal by the Wiggers' procedure (27). In such a preparation, Fredlund et al (17) and Becker et al (19) found that hemorrhage led to hypokalemia, a result opposite to that observed in the present investigation and in the studies of Stremple et al (16). In a similar anesthetic preparation, Wright (13) found that hemorrhagic hypotension led to an increase in plasma phosphate concentration.

In species other than swine, a variety of electrolyte alterations have been recorded. It would appear that the first such study was reported in 1926 by Kerr (55). He found that removal by cardiac puncture of a third to half the blood volume of conscious dogs caused a decrease in plasma sodium and chloride concentrations but no significant change in the plasma concentrations of potassium, calcium, or magnesium. Interestingly, he also recorded a marked increase in erythrocyte potassium concentration after hemorrhage. The meaning of this alteration is difficult to ascertain since sodium is the principal intracellular cation in the erythrocytes of dogs, in contrast to pigs and humans in which potassium is the principal intracellular cation (56). Kerr (55) attributed the plasma electrolyte alterations to a shift of tissue fluids to the vasculature; he could find no simple explanation for the accumulation of potassium by erythrocytes. By World War II the methods for measuring plasma electrolyte concentrations were far superior to those utilized by Kerr; because of this a clearer picture emerged of electrolyte metabolism in the hemorrhaged animal. These later studies were concerned primarily with sustained hypotension and shock. The most extensive work was reported by Root et al (57) who observed in dogs that hemorrhage caused increases in plasma potassium, magnesium, phosphate, and lactate concentrations, but had little or no effect on sodium, calcium, or chloride concentrations. Elevated plasma potassium levels during the terminal stages of hemorrhagic shock have been reported by a number of investigators (58-64). Less frequently, terminal increases in magnesium (61) and phosphate (65,66) have been observed. In most instances, these changes were seen during the terminal stages of

hemorrhagic hypotension; hence they have been attributed to suppression of adenosine triphosphate synthesis, degradation of intracellular organic phosphates, and failure of cellular transmembrane ion transport systems (e.g., Na/K, ATP-ase), especially in liver tissue (2,4,5,57,60,67-72).

Up to the present time no one has proposed a mechanism that could account for posthemorrhagic hypokalemia seen here and occasionally in other studies of hemorrhagic hypotension (16,73,74). A clue to its nature, however, is suggested by the significant negative correlation found between plasma glucose and potassium concentrations during the early recovery period (Table 5). A similar relationship was noted also by Linberg et al (75) in trauma patients and for 50 years or more under a variety of other experimental circumstances (76). Such studies have shown, for example, that epinephrine injections lead not only to hepatic glycogenolysis and hyperglycemia, but also to a brief transient hyperkalemia followed by prolonged hypokalemia (76-78). The latter was attributed by early workers to enhanced glucose uptake by skeletal musculature and a concomitant muscle uptake of potassium (76). Other investigators reported that insulin injections caused a reduction in blood glucose levels that were accompanied by reductions in plasma potassium and phosphate; since the latter two effects were of the same order of magnitude, they concluded that potassium was a key component of glucose phosphorylation (79,80). In support of these concepts, Dury (81) showed in rats that injection of epinephrine followed by injection of glucose led to concomitant hyperglycemia, hypokalemia, and an increase in muscle, but not liver, potassium concentration. Recently, Flatman and Clausen (82) found that intravenous glucose injections led to hypokalemia associated with an increase in plasma insulin concentration. Earlier, they had shown with an *in vitro* soleus muscle preparation that both insulin (83) and epinephrine (84) stimulated the Na<sup>+</sup>-K<sup>+</sup> pump leading to an increase in intracellular potassium, a decrease in intracellular sodium, and an increase in membrane potential. These effects of epinephrine and insulin, furthermore, were additive (82). In addition, Randle and Smith (85) found in an *in vitro* diaphragm preparation that cellular glucose uptake was markedly enhanced by anaerobic conditions. When insulin was included in the incubation medium, glucose uptake under aerobic conditions increased to the same level as that seen under anaerobic conditions (85). Anaerobiosis, therefore, had an insulin-like effect.

On the basis of the forgoing observations, we suggest the following hypothesis to account for the hypokalemia that follows 50 percent blood loss. Hemorrhagic hypotension causes an increase in adrenal epinephrine secretion which in turn leads to hyperglycemia. Hemorrhagic hypotension also leads to reduced cardiac output and proportionately far greater reduced blood flow and oxygen transport to the skeletal musculature. The latter effects cause a marked increase in anaerobic glucose utilization, and concomitant potassium accumulation, by muscle tissue. Metabolic acidosis associated with

hemorrhagic hypotension would enhance these effects, but an increase in plasma insulin concentration would not be required for this mechanism to be operative; in fact, the effects of hemorrhagic hypotension on plasma insulin concentrations and actions are equivocal (12).

#### Plasma Enzymes:

The effects of hemorrhage on plasma enzyme concentrations reported here are in distinct contrast to those reported by others. No evidence of tissue damage, as evidenced by an increase in enzyme concentration, was found in conscious pigs subjected to either 30 or 50 percent blood loss. In fact, the plasma concentrations of most enzymes were decreased after hemorrhage. These decrements would appear attributable to the transfer of fluid from the extra- to the intravascular compartment that was noted earlier in the same animals (9).

Most workers have found that the plasma concentrations of various enzymes increase after hemorrhage. In anesthetized, mechanically ventilated swine, Fredlund and his colleagues (17,18,20) thus reported increases in the serum concentrations of beta-glucosidase, beta-galactosidase, and glutamic-oxalacetic transaminase after hemorrhagic shock induced by the Wiggers' procedure (27). In the same type of preparation, Vesell et al (86) found increases in the serum concentrations of lactic and malic dehydrogenase, glutamic-oxalacetic transaminase, and alkaline phosphatase of dogs, and lactic dehydrogenase of rabbits during hemorrhagic shock. In anesthetized cats Rosenfeld (87) found increases in serum cathepsin D and alkaline phosphatase during sustained hypotension. Increases in serum alpha-glucosidase were reported by Forsyth et al (88) for conscious, restrained monkeys subjected to repeated hemorrhages. The divergence of the forgoing results from those obtained in the present study would appear attributable to differences in experimental conditions. In this respect, the impact of anesthesia, the Wiggers' procedure (27), and physical restraint on the hemodynamic and acid-base responses of animals to hemorrhage have been discussed in earlier reports of this series (8,9).

#### CONCLUSIONS

Hemorrhage in the conscious unrestrained pig leads to transient hyperglycemia which would appear to be attributable to elevated adrenomedullary epinephrine secretion and consequent hepatic glycogenolysis.

Hemorrhage also leads to lactacidemia which is attributable increased anaerobic glycolysis in the skeletal musculature.

Increased muscle glucose utilization after hemorrhage causes hypokalemia, but the precise mechanism remains obscure.

Transient creatinemia after hemorrhage would appear attributable to reduced renal clearance while progressive uremia would appear attributable to increased protein catabolism and hepatic urea synthesis.

The magnitude of posthemorrhage hyperglycemia, lactacidemia, creatininemia, and plasma magnesium increments is determined by the degree of arterial blood pressure and bicarbonate decrements.

#### RECOMMENDATIONS

The plasma concentrations of epinephrine, insulin, glucagon, cortisol, and norepinephrine should be determined in the conscious pig subjected to hemorrhage.

The effects of hemorrhage on concentrations of blood amino acids, uric acid, and ammonia should be determined in conscious pigs.

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## LEGENDS OF TABLES

- Table 1 Two-Factor Analysis of Variance Summary: Three Groups
- Table 2 Two-Factor Analysis of Variance Summary: Group Pairs
- Table 3 Single Factor Analysis of Variance Summary for Time
- Table 4 Effects of 30 and 50 Percent Blood Loss and Spontaneous Recovery Therefrom on Plasma Enzyme Levels of Conscious Pigs
- Table 5 Correlation Matrix: Interrelationships of Hemodynamic, Acid-Base, Metabolite, and Electrolyte Alterations Subsequent to 30 and 50 Percent Blood Loss

APPENDIX

Table 1. Two-factor analysis of variance summary: three groups

	Group	F-Ratio Time	G x T
Glucose	21.88*	5.27*	2.89*
Lactate	15.72*	16.32*	11.69*
Urea	1.68	10.63*	14.82*
Creatinine	2.71	12.18*	7.46*
Sodium	0.26	1.57	0.38
Potassium	3.62*	4.64*	2.18*
Magnesium	1.87	0.30	2.40*
Phosphate	1.17	1.65	0.91

\*Indicates significant ( $P < 0.05$ ) effect: Group,  $F_{2,15}=3.68$ ;

Time,  $F_{7,105}=2.09$ ; G x T,  $F_{14,105}=1.78$

Table 2. Two factor analysis of variance summary: group pairs

	Pair	Group	F-Ratio Time	G x T
Glucose	C x 30	6.93*	4.32*	2.36*
	C x 50	30.68*	3.41*	3.30*
	30 x 50	18.47*	6.00*	2.52*
Lactate	C x 30	2.99	12.55*	7.58*
	C x 50	15.80*	12.55*	11.86*
	30 x 50	16.09*	18.23*	11.66*
Urea	C x 30	1.76	0.32	2.60*
	C x 50	3.83	14.01*	34.89*
	30 x 50	0.06	21.71*	12.23*
Creatinine	C x 30	0.96	0.99	1.05
	C x 50	4.28	11.05*	11.14*
	30 x 50	2.19	15.12*	7.02*
Sodium	C x 30	0	1.49	0.68
	C x 50	0.26	1.57	0.38
	30 x 50	0.32	0.95	1.12
Potassium	C x 30	3.64	0.75	0.32
	C x 50	8.11*	4.25*	2.24*
	30 x 50	0.08	5.33*	3.19*
Magnesium	C x 30	1.84	0.30	2.40*
	C x 50	1.04	3.14*	2.16*
	30 x 50	3.57	2.35*	3.86*
Phosphate	C x 30	2.07	1.14	1.65
	C x 50	0.08	0.88	0.97
	30 x 50	2.68	2.11	0.63

\*Indicates significant ( $P < 0.05$ ) effect: Group,  $F_{1,10} = 4.96$ ;

Time,  $F_{7,70} = 2.14$ ; G x T,  $F_{7,70} = 2.14$

Table 3. Single factor analysis of variance summary for time

	Group	F-Ratio
Glucose	Control	0.66
	30% Hemorrhage	5.81*
	50% Hemorrhage	4.18*
Lactate	Control	2.01
	30% Hemorrhage	14.46*
	50% Hemorrhage	14.95*
Urea	Control	3.56*
	30% Hemorrhage	0.79
	50% Hemorrhage	39.42*
Creatinine	Control	0.66
	30% Hemorrhage	1.33
	50% Hemorrhage	15.16*
Sodium	Control	1.00
	30% Hemorrhage	1.16
	50% Hemorrhage	0.90
Potassium	Control	0.40
	30% Hemorrhage	0.72
	50% Hemorrhage	5.39*
Magnesium	Control	1.40
	30% Hemorrhage	1.19
	50% Hemorrhage	3.42*
Phosphate	Control	0.43
	30% Hemorrhage	2.06
	50% Hemorrhage	1.17

\*Indicates significant ( $P < 0.05$ ) effect:  $F_{7,35} = 2.29$

Table 4. Effects of 30 and 50 percent blood loss and spontaneous recovery therefrom on plasma enzyme levels of conscious pigs

Experimental Group	Spontaneous Recovery (min)			
	Control	0	60	300
Alanine Transaminase				
Control Group	27.0+2.04	27.0+1.65	26.9+1.91	27.4+1.38*
30% Hemorrhage	25.3+1.29	23.5+1.31*	22.6+1.52*	22.3+1.38*
50% Hemorrhage	23.5+2.04	20.9+1.79*	20.9+1.60*	22.5+1.22
Aspartate Transaminase				
Control Group	19.3+1.94	19.5+1.88	18.5+1.74	20.8+2.08
30% Hemorrhage	16.3+1.18	16.1+1.09	14.8+0.99	15.6+0.68
50% Hemorrhage	18.5+1.37	17.3+1.07	17.3+2.18	22.1+3.51
Lactic Dehydrogenase				
Control Group	179+14.6	184+14.5	186+12.6*	231+11.8*
30% Hemorrhage	179+10.9	164+ 5.3*	162+ 7.4*	204+16.9*
50% Hemorrhage	176+13.4	160+13.0*	160+14.8*	201+21.3*
Creatine Kinase				
Control Group	53+ 8.3	51+ 7.7	48+ 8.6	55+ 6.3
30% Hemorrhage	67+10.1	53+ 8.2	49+ 8.5	57+13.1
50% Hemorrhage	62+ 4.5	62+11.2	79+30.4	75+18.4
Alkaline Phosphatase				
Control Group	68+8.4	70+8.1	70+9.1	73+9.6
30% Hemorrhage	65+4.7	62+4.5	60+4.8*	61+4.2*
50% Hemorrhage	70+8.1	65+7.2	66+5.9	70+6.9

All Values expressed as mean  $\pm$  SEM, International units/ml

\*Indicates significant ( $P < 0.05$ ) difference from initial control value, as determined by repeated measures analysis of variance.

Table 5. Correlation matrix: Interrelationships of hemodynamic, acid-base, metabolite, and electrolyte alterations subsequent to 30 and 50 percent blood loss

	$P_a$	$HCO_3^-$	Gluc	Lact	Creat	$K^+$
$HCO_3^-$	0.681*					
Gluc	-0.667*	-0.549*				
Lact	-0.830*	-0.887*	0.613*			
Creat	-0.652*	-0.728*	0.491	0.791*		
$K^+$	0.129	0.054	-0.604*	-0.288	-0.091	
$Mg^{++}$	-0.687*	-0.365	0.769*	0.620*	0.398	0.361

\*Indicates significant ( $P < 0.05$ ) relationship:  $df=10$ ,  $r=0.497$

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