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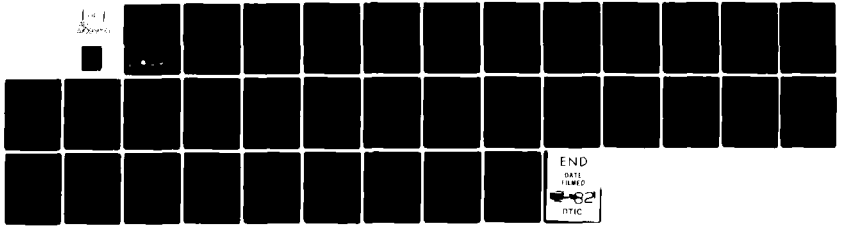

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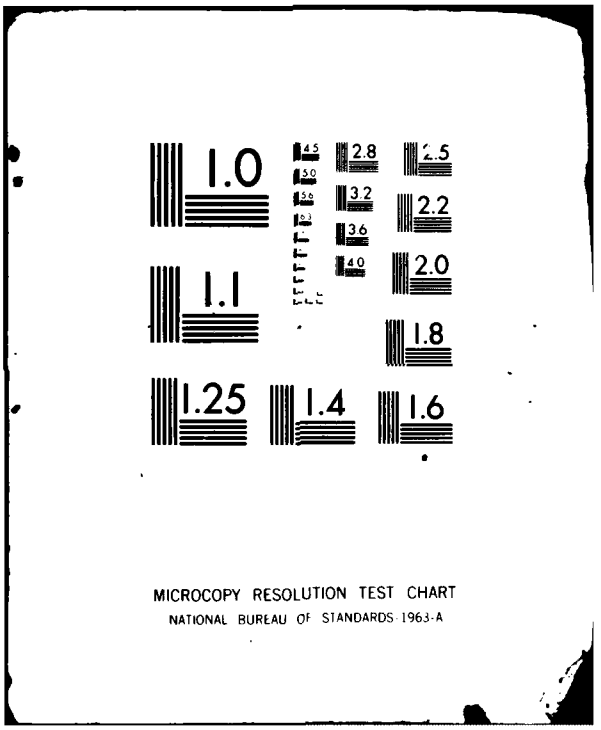
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PHYSIOLOGIC ASPECTS OF PORCINE HEMORRHAGE

IV. *Blood Gas and Acid-Base Status of the Conscious Animal Following 30 and 50 Percent Blood Loss*

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Physiologic Aspects of Porcine Hemorrhage. IV. Blood gas and acid-base status of the conscious animal following 30 to 50 percent blood loss--Hannon et al

In conducting the research described in this report, the investigation adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care, Institute of Laboratory Animal Resources, National Research Council.

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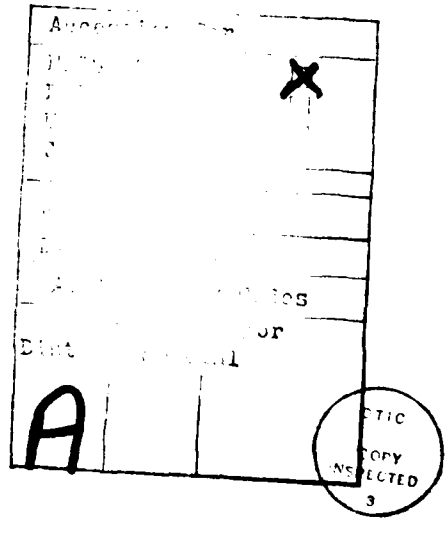
20. Abstract

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 arterial blood gas and acid-base status in the absence of anesthesia or other interventions. Chronic catheters were placed surgically in the aorta, via the carotid artery, in three groups (n=6/group) of young, domestic pigs. Seven to ten days after surgery, each animal was brought into the laboratory and the catheter was connected to a three-way stopcock and pressure transducer for blood removal and hemodynamic recording. After 30 minutes of unrestrained and uninterrupted supine rest, control measurements were made every 10 minutes for the next 30 minutes. Thereafter, the pig was subjected to one of three 1-hour treatments: 30 percent loss of the estimated blood volume; 50 percent blood loss; or left undisturbed (control group). Subsequent to the hemorrhage or control period, all measurements were repeated at 0, 30, 60, 120, 180, 240 and 300 minutes of spontaneous recovery. Immediately after the hemorrhage episode, the blood gas and acid-base status of pigs subjected to 30 percent hemorrhage was unaltered relative to their own control values or the values recorded in the control group of pigs. Fifty percent blood loss led to a metabolic acidosis that was largely compensated. Accordingly, the group mean for blood pH decreased slightly, from 7.500 to 7.464, P CO_2 from 41.0 to 28.4 torr, [HCO_3^-] from 31.0 to 21.0 mEq/l, and base excess from 8.1 to -1.3 mEq/l, while arterial P O_2 rose from 79.7 to 98.8 torr. During the 5-hour period of spontaneous recovery, all the foregoing changes reverted to and eventually exceeded values recorded in the initial control period or in the control group measured at the same time point of recovery. Except for arterial P O_2, which remained at control levels, the acid-base values of pigs subjected to 30 percent hemorrhage also rose and eventually exceeded control levels as the period of spontaneous recovery progressed. On the basis of linear regression and correlation analysis, it appears that arterial chemoreceptor drive for ventilation became inoperative during and for five hours after hemorrhage. These analyses also indicate that baroreceptor drive of heart rate was eliminated during hemorrhage but returned during spontaneous recovery.

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 arterial blood gas and acid-base status in the absence of anesthesia or other interventions. Chronic catheters were placed surgically in the aorta, via the carotid artery, in three groups (n=6/group) of young, domestic pigs. Seven to ten days after surgery, each animal was brought into the laboratory and the catheter was connected to a three-way stopcock and pressure transducer for blood removal and hemodynamic recording. After 30 minutes of unrestrained and uninterrupted supine rest, control measurements were made every 10 minutes for the next 30 minutes. Thereafter, the pig was subjected to one of three 1-hour treatments: 30 percent loss of the estimated blood volume; 50 percent blood loss; or left undisturbed (control group). Subsequent to the hemorrhage or control period, all measurements were repeated at 0, 30, 60, 120, 180, 240 and 300 minutes of spontaneous recovery. Immediately after the hemorrhage episode, the blood gas and acid-base status of pigs subjected to 30 percent hemorrhage was unaltered relative to their own control values or the values recorded in the control group of pigs. Fifty percent blood loss led to a metabolic acidosis that was largely compensated. Accordingly, the group mean for blood pH decreased slightly, from 7.500 to 7.464, P CO_2 from 41.0 to 28.4 torr, [HCO_3^-] from 31.0 to 21.0 mEq/l, and base excess from 8.1 to -1.3 mEq/l, while arterial P O_2 rose from 79.7 to 98.8 torr. During the 5-hour period of spontaneous recovery, all the foregoing changes reverted to and eventually exceeded values recorded in the initial control period or in the control group measured at the same time point of recovery. Except for arterial P O_2, which remained at control levels, the acid-base values of pigs subjected to 30 percent hemorrhage also rose and eventually exceeded control levels as the period of spontaneous recovery progressed. On the basis of linear regression and correlation analysis, it appears that arterial chemoreceptor drive for ventilation became inoperative during and for five hours after hemorrhage. These analyses also indicate that baroreceptor drive of heart rate was eliminated during hemorrhage but returned during spontaneous recovery.



PREFACE

This is the fourth in a series of reports on the physiologic responses of domestic swine to hemorrhagic hypotension. Earlier reports were concerned with chronic catheterization techniques and the hemodynamic responses of conscious animals to moderate and severe blood loss. In the future, the series will describe the metabolite, electrolyte, plasma protein, and body fluid alterations of these animals.

We wish to express our appreciation for the conscientious and dedicated technical assistance provided by SFC Marshall F. Jones, SSG Maria DeLaCerda, PFC Robert J. Hughes, SP4 David Weber, and SP4 Nancy Champagne in the surgical preparation of the animals, and Diane G. Arevalo for her care during all stages of the study. We are also highly indebted to Dr. Virginia Gildengorin for her invaluable assistance in statistical evaluation of the data, Sue Davis for the numerous hours she spent 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
IV. BLOOD GAS AND ACID-BASE STATUS OF THE CONSCIOUS ANIMAL FOLLOWING 30 AND 50 PERCENT BLOOD LOSS

In a previous report (1), we described the arterial pressure, heart rate, and hematocrit changes associated with 30 and 50 percent hemorrhage of the estimated blood volume of conscious young domestic swine. Mild hypotension was recorded immediately after 30 percent blood loss and severe hypotension after 50 percent blood loss. During the subsequent five-hour spontaneous recovery, arterial pressures returned to control levels in the 30 percent group but only partially so in the 50 percent group. In both, spontaneous recovery of arterial pressure was attributable to two factors: a progressive increase in heart rate commencing about 30 minutes after cessation of hemorrhage, and hemodilution commencing during blood loss and increasing in degree as spontaneous recovery progressed. All pigs in both groups were alive, alert, and hungry 24 hours after hemorrhage.

In the present study, the blood gas and acid-base changes exhibited by these same two groups of pigs after hemorrhage and during spontaneous recovery are described. Data show that hemorrhagic hypotension leads to metabolic acidosis which is compensated by a depletion of bicarbonate buffer stores. Spontaneous recovery initially entails ventilatory removal of carbon dioxide so produced and ultimately restoring normal blood acid-base characteristics.

Historical Background: Since the turn of the century, or before, shock states including those induced by hemorrhage have been associated with alterations in the acid-base status of the body (2). For many years, the exact nature of these alterations remained controversial. This was attributable to technological limitations which precluded accurate measurements of the requisite variables, but it was perpetuated by conceptual differences among the proponents of various theories of acid-base regulation. One of the first studies was reported in 1895 by Viola and Jona (3), who found that the titratable alkalinity of plasma was reduced transiently when dogs were subjected to a blood loss of about 40 ml/kg. They attributed this effect to an increase in tissue acid production, its migration to the blood, and its subsequent neutralization (3). In contrast, other early workers, noting a reduction in total carbon dioxide content of the blood, i.e., alkali reserve, felt that acidosis was the cause—not the result—of the circulatory deterioration which characterized severe shock stages. Spiro (4), for example, showed in 1902 that intravenous administration of hydrochloric acid in rabbits or sodium acid phosphate in dogs, both

of which reduced blood carbon dioxide content, was followed by typical shock effects. Howell in 1904 (5) claimed that intravenous sodium carbonate infusions beneficially affected animals in shock and took the view that this primarily was due to its action on the heart. Similar results and interpretations were reported by Dawson (6) and Seelig et al (7) who used bicarbonate infusion to counteract acidosis. An alternate opinion was expressed in 1910 by Yandell Henderson (8) who, upon noting hyperpnea in shocked animals, attributed the decreased alkali reserve to hyperventilation; a similar effect had been seen consistently in high altitude sojourners and was termed at the time "acapnia." Henderson and his colleagues maintained this opinion for many years (9-11) and attempted to show that hyperventilation caused the alkali reserve to migrate with fluid from the blood to the tissues, thus accounting for the oligemia seen in traumatic shock. According to this concept, tissues of the shocked individual became alkalotic rather than acidotic. Gesell (12), however, showed in 1919 that after either hemorrhage or visceral trauma, the reduction in blood alkali reserve was compensated by a transfer of alkali from the tissues to the blood. Despite his interpretational errors with respect to acid-base regulation, it is interesting to note that Henderson was the first investigator to attribute the circulatory deterioration of shock to an inadequate venous return (8).

The majority of workers in this era held that shock states were associated with excessive fixed-acid production and this in turn caused an increase in hydrogen ion concentration and a reduction in alkali reserve (1,2,11-14). That alkali reserve could be reduced without an increase in hydrogen ion concentration, was scarcely considered by most workers, largely because the decrements were so pronounced and available procedures for measuring blood hydrogen ion concentration lacked precision and accuracy. This attitude persisted for many years (13-15) despite the demonstration in 1909 by L.J. Henderson (16) that ventilatory CO_2 elimination played a major role in compensating for excessive production of tissue acid and thus the maintenance of blood neutrality. A few workers clearly recognized the role that ventilation played in the shocked individual. Walter B. Cannon (17), for example, in his studies of battlefield injuries and shock during World War I stated: "The H-ions of the blood do not increase to an important degree, therefore, in spite of reduced alkali, if pulmonary ventilation prevents the accumulation of carbonic acid."

About 1920, insight began to emerge into the precise nature of the acid-base disorders associated with shock. Key information was provided in 1921 by Macleod (18), who showed that the previously assumed production of lactic acid in shock did indeed occur, but not until shock had become irreversible, i.e., when both respiratory and circulatory functions were markedly depressed. He concluded, correctly, that production of lactic acid was the result of tissue anoxemia; hence lactacidemia was not the cause, but rather the result of shock. Macleod's (18) observations and conclusions have been

confirmed repeatedly in studies of hemorrhagic shock in laboratory mammals (19-25) and humans (26-29).

A second major advance in the understanding of acid-base physiology in the shocked organism was reported in 1927 by Hertzman and Gesell (30). They showed with manganese dioxide and hydrogen electrodes that hemorrhage lowered the pH of venous blood, an effect they attributed to inadequate tissue blood flow, reduced oxidative metabolism and, consequently, increased fixed-acid production. Simultaneous measurements of arterial blood, however, showed in most instances that hemorrhage caused the pH to increase and that such increases were attributable to hyperventilation. Arterial pH only decreased in severe shock when pulmonary ventilation was depressed. These observations by Hertzman and Gesell (30) firmly established the important compensatory role of ventilation in regulating acid-base status during hemorrhagic shock. Reduced alkali reserve, therefore, did not necessarily signal a reduced hydrogen ion concentration, at least insofar as arterial blood was concerned. Reduced arterial pH values would only be seen if fixed-acid production outstripped blood buffering capacity and the pulmonary capacity to eliminate the carbon dioxide that was liberated from bicarbonate. Subsequent investigations have been in general agreement with the observations of Hertzman and Gesell, even though most workers directed their attention to severe or irreversible shock. In both experimental animals (19,31-33) and humans (26,34,35), severe or irreversible shock was usually associated with reduced pH values. However, increased arterial pH values were a common finding during the early stages of hypovolemia when $P_a CO_2$ and alkaline reserve (bicarbonate concentration) were still relatively high, i.e., before tissue metabolic functions had been seriously impaired (36-42). Not all workers, it should be noted, attributed elevated arterial pH values to hyperventilation. Pardy and Dudley (38), for example, contended that metabolic depression with attendant reduction of carbon dioxide production was the primary causative factor. Their arguments favoring this mechanism, however, were weakened by the lack of data on mixed venous carbon dioxide tension; hence the pulmonary capillary-alveolar pressure gradient for ventilatory carbon dioxide elimination was unknown.

A third major advance in the acid-base physiology of hemorrhaged animals was reported in 1947 by Root et al (43). They were the first to attempt to measure simultaneously all the major blood factors contributing to acid-base balance. Dogs were subjected to blood volume losses ranging from 29-56 percent, causing arterial P CO_2 and pH values to decrease. Total serum cations (Na + K + Ca + Mg) rose slightly as a result of hemorrhage, the increase being attributable to elevated values for potassium and magnesium. On the anion side of the serum electrolyte ledger, shock was associated with reduced values for bicarbonate and proteinate, sizably increased values for lactate and phosphate, slightly increased values for pyruvate and sulfate, but no change in chloride levels. Significantly, they showed that the total

cation--total anion difference, i.e., the anion gap, expanded in the shocked animal and concluded that this must mean that fixed acids were produced, other than lactate, pyruvate, sulfate, and phosphate. What these might be is still a subject of speculation since no one, insofar as we are aware, has attempted to replicate the experiments of Root et al (43) with the added purpose of identifying the nature of additional fixed acids produced during shock. Instead, most workers in recent years have described acid-base status in terms of pH, P CO_2, and the concentration of bicarbonate, lactate, and base excess. With respect to the latter, hemorrhagic hypotension, as might be anticipated, almost invariably led to negative values (38,39,44). Recent attention has been directed also to the effects of hemorrhage on pulmonary gas exchange (33,36,45-47) and, insofar as acid-base status was concerned, deleterious effects have been attributed to hypoxemia resulting from inadequate alveolar-pulmonary capillary oxygen transfer (46). Such transfer defects could have been caused by pulmonary edema and resultant impairment of oxygen diffusion (45) or platelet aggregation and distortion of normal ventilation/perfusion characteristics (48).

Porcine Studies: Few investigations of acid-base regulation after hemorrhagic shock have been conducted in conscious animals and fewer still in conscious swine. The preponderance of large-animal studies have employed dogs as a biomedical model. In most instances, furthermore, anesthesia was used during the induction of hemorrhagic hypotension and shock. The few swine studies that are reported were of limited scope insofar as blood gas and acid-base measurements were concerned, and all but one of these studies employed anesthetized pigs as an animal model. This seems rather surprising in view of the apparent superiority of the conscious pig, relative to the dog, as a model for acquiring functional data that are applicable to man (49,50). Anesthetized swine subjected to hemorrhagic hypotension were shown by Lindberg (51) to exhibit decreased arterial pH and standard bicarbonate which were attributable to increases in lactic acid concentration. Fredlund's laboratory, in a series of studies (52-54), also recorded reduced arterial pH and bicarbonate values and increased lactate values but little or no change in arterial P O_2 or P CO_2. The physiologic significance of these observations is difficult to assess, first because the responses to hemorrhage were probably modified by anesthesia (49), second because normal compensatory responses operating during hypotension were seriously distorted, if not eliminated, by using the Wiggers' procedure (55) to induce shock, and third because pulmonary carbon dioxide elimination was regulated with a mechanical ventilator. A similar animal preparation was used by Norton et al (56) to study stress ulcer formation. They reported that death during hemorrhagic hypotension was associated with respiratory alkalosis and that this was attributable to excessive mechanical ventilation; no acid-base measurements were reported for surviving animals. Becker et al (57), in experiments patterned after those of Norton et al (56), recorded low base excess values in anesthetized mechanically ventilated animals subjected to sustained hemorrhagic hypotension for three hours.

In the absence of mechanical ventilation, anesthetized swine subjected to hemorrhagic hypotension according to the Wiggers procedure (55) were shown by Lowery and Sugg (48) to exhibit hyperventilation with reduced arterial P CO_2 and elevated arterial P O_2 values. Such animals were reported also by Noble (45) to show metabolic acidosis and reduced arterial pH, but the values were not presented. Anesthetized pigs subjected to traumatic shock with ventilation controlled to maintain a normal arterial P CO_2 were shown by Rokkanen et al (58) to exhibit a progressive fall in arterial pH, base excess, and standard bicarbonate concentrations, and an increase in arterial lactate concentration. The only study, insofar as we are aware, containing acid-base measurements made on unanesthetized pigs was reported by Orringer and Carey (59). They showed that hemorrhagic hypotension produced by the Wiggers procedure (55) led to an increase in arterial lactate concentration. Unfortunately, no other acid-base variables were included in their measurements.

METHODS

Eighteen young domestic swine, both barrows and gilts, were used in this study. They were distributed to three groups, each containing six animals; one served as a control, a second was subjected to 30 percent hemorrhage, and the third was subjected to 50 percent hemorrhage. Previously we have reported details of the procurement, housing, surgical implantation of chronic catheters, postsurgical treatment, hemorrhage procedure, and experimental conditions associated with data collection from these pigs (1,49).

Blood gas and acid-base measurements were made on arterial samples taken at the same timepoints as the previously reported hemodynamic measurements (1). Briefly, baseline control values were obtained in duplicate or triplicate at 10-minute intervals subsequent to at least 30 minutes of unrestrained recumbant rest. Thereafter, the animals were hemorrhaged for one hour to achieve 30 or 50 percent loss of the estimated blood volume or, in the case of the controls, remained undisturbed for a similar period. Subsequently, post-hemorrhage or control samples for blood gas and acid-base measurements were taken at 0, 30, 60, 120, 180, 240, and 300 minutes.

Blood gas and acid-base measurements were made at 38C with an Instrumentation Laboratory, Model 813 automated analyzer (Instrumentation Laboratories, Inc., Lexington, MA). The pH electrode was calibrated with precision buffer solutions (pH 6.840 and 7.384) prepared by Instrumentation Laboratory. The analyzed gases ($\pm$ 0.03% tolerance) used to calibrate the P O_2 and P CO_2 electrodes were prepared also by Instrumentation Laboratory. The dead space in the syringes used to obtain blood samples was filled with heparin solution, 1000 units/ml, and the blood gas and acid-base measurements were made immediately after blood withdrawals.

Data from all three groups were first evaluated with two-factor (condition x time) analyses of variance. Next, significant main effect 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, least-squares linear regression values and Pearson Product-Moment correlation values for data obtained from the hemorrhaged pigs were computed immediately after the bleeding episode and after five hours of spontaneous recovery. Included in these computations were all data (except base excess) reported here plus the heart rate and mean arterial data reported earlier (1) for the same animals. In all statistical computations, significant effects were assumed when $P \leq 0.05$.

RESULTS

Mean values for the pH and blood gas changes associated with 30 and 50 percent loss of the estimated blood volume, and spontaneous recovery therefrom, are illustrated in Figure 1. Mean values for the bicarbonate and base excess changes are illustrated in Figure 2. Control values are included in both figures. Data reported in the following text are expressed as the mean $\pm$ SEM. Tables 1-3 summarize the F ratios obtained from analysis of variance evaluation of all data recorded during the study. Table 1 simultaneously compares all three groups, Table 2 the groups taken in pairs, and Table 3 the individual groups relative to the time factor.

Arterial pH: During the initial control period, pH values for the three groups were essentially equal (Figure 1). The control group had a mean value of 7.499 $\pm$ 0.0024 and the values did not deviate significantly from this level for the ensuing 6-hour experimental period. Hemorrhage and recovery, however, were associated with small but significant changes in arterial pH; foremost was a decrease from 7.500 $\pm$ 0.0043 to 7.464 $\pm$ 0.0099 immediately after 50 percent blood loss. The values in this group remained low during the first 30 minutes of the recovery period and then gradually reverted to control levels over the remainder of the recovery. The hemorrhage-induced decrease and subsequent reversion seen in this group of pigs account for the time and group X time interactions seen in Tables 2 and 3. Pigs subjected to 30 percent hemorrhage showed no significant pH changes immediately after the hemorrhage episode, but their values tended to rise slightly (to 7.513 $\pm$ 0.009 from 7.499 $\pm$ 0.0057) over the course of the recovery period. This tendency was not statistically significant when evaluated by a single factor analysis of variance (Table 3), but it did yield a significant group X time interaction when data from the 30 percent hemorrhage and control groups were evaluated with a two-factor analysis of variance (Table 2). Thus, as a function of time, the values in this hemorrhage group rose significantly, relative to the values in the control group.

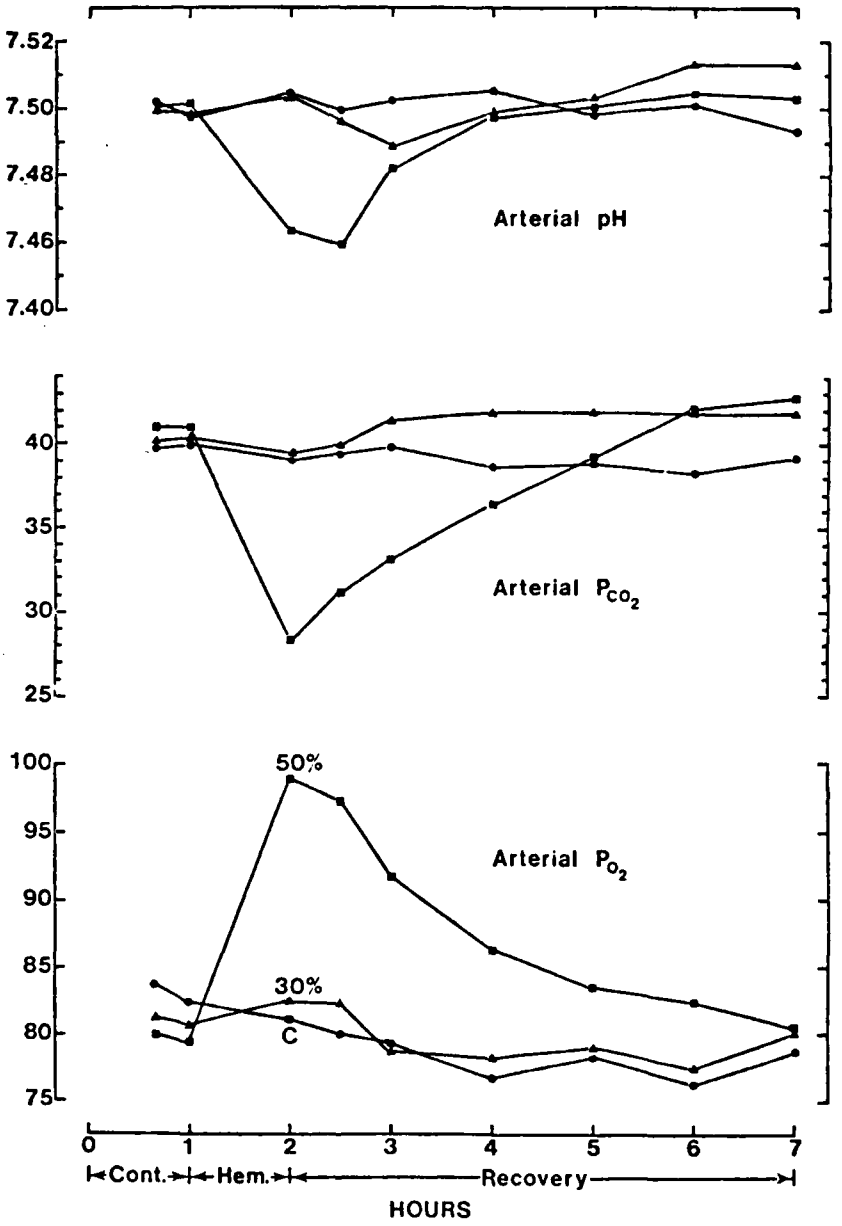

Figure 1. Effects of 30% and 50% blood loss on the pH, P_{CO_2}, and P_{O_2} of arterial blood of conscious young domestic swine. C refers to control animals (N = 6 pigs/group). Ordinate values in pH units and mm Hg.

Arterial P CO_2: The control animals had an initial P CO_2 value of 40.0 ± 0.86 torr and did not deviate significantly from this level during the experimental period (Figure 1). The hemorrhaged animals had similar initial levels, but subsequent to hemorrhage significant group, time and group X time effects were recorded. The most prominent change was the post-hemorrhage decrease, from 41.0 ± 1.17 to 28.4 ± 1.90 torr, seen in the 50 percent group; the immediate post-hemorrhage values in the 30 percent group were unaltered. Over the course of the recovery period, the values in both hemorrhage groups rose to, and eventually exceeded slightly, those observed in the control animals. These increments account for the significant time and group X time interactions recorded in Tables 2 and 3. Thus, at the end of the recovery period, the mean values for the 30 and 50 percent groups were 41.8 ± 0.51 and 42.7 ± 0.42 torr, respectively, and were both signficantly above the 39.1 ± 0.93 torr recorded at the same time point for the control group.

Arterial P O_2: A progressive and significant decrease in arterial P O_2 of the control pigs was observed over the course of the experimental period (Figure 1, Table 3). Accordingly, from a control level of 83.1 ± 0.75 torr the mean values decreased to a nadir of 76.1 ± 1.03 torr at hour 6. The terminal mean was 78.6 ± 1.69 torr. Pigs subjected to 30 percent hemorrhage, as a group, showed changes over the course of the experimental period that were no different statistically from those shown by the control pigs (Tables 2, 3). In distinct contrast to the foregoing, 50 percent hemorrhage led to a significant rise in arterial P O_2, from a control level of 79.7 ± 1.15 torr to an immediate post-hemorrhage level of 98.8 ± 2.39 torr. Subsequently, the values reverted to control levels over the course of recovery. This reversion led to the significant time and group X time effects seen in the analyses of variance tables; i.e., as a function of time the response of the 50 percent group was significantly different from the other two groups.

Arterial [HCO_3^-]: From the control through the experimental period, bicarbonate values in the control pigs remained unaltered (Figure 2). Furthermore, the initial value for the group 29.9 ± 0.69 mEq/l, was not significantly different from the prehemorrhage values recorded in the other two groups of pigs. The only immediate effect of hemorrhage was a significant decrease in the bicarbonate concentration of the 50 percent groups, from 31.0 ± 0.60 to 21.0 ± 2.09 mEq/l (Tables 1, 2). Over the recovery period the values reverted to and ultimately exceeded those recorded before hemorrhage, i.e., to 32.6 ± 0.76 from 31.0 ± 0.60 mEq/l, as well as those recorded at the same time points in the control pigs. This reversion accounted for the significant time and group X time interactions recorded in Tables 2 and 3 for the two groups. Pigs subjected to 30 percent hemorrhage also showed a significant increase (from 30.4 ± 0.52 to 32.7 ± 0.63 mEq/l) in bicarbonate concentration over the course of the recovery (Table 3), and this produced a significant group X time interaction when they were

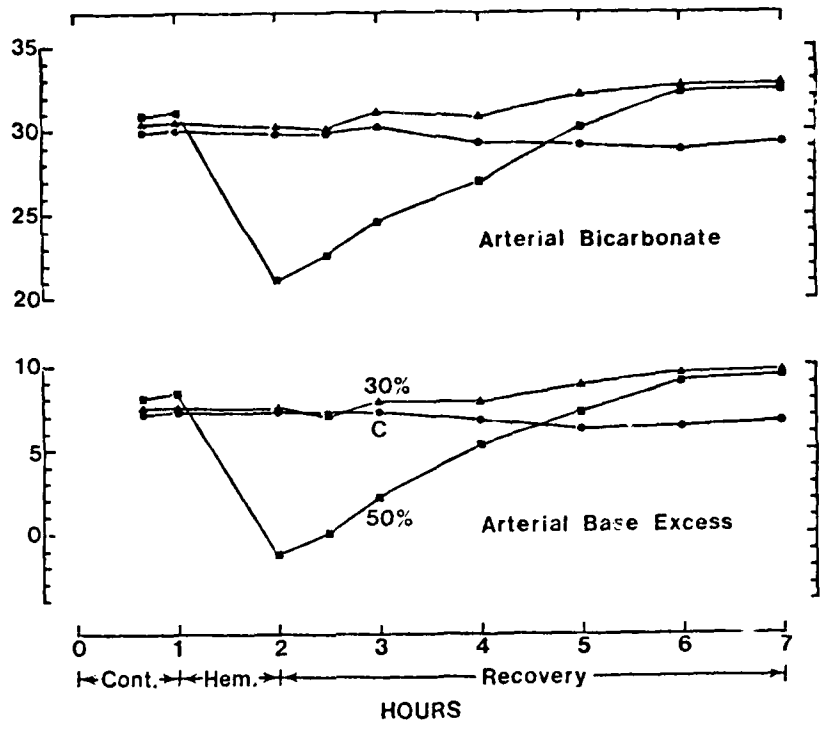

Figure 2. Effects of 30% and 50% blood loss on the bicarbonate and base excess concentrations of arterial plasma. C refers to control animals (N = 6 pigs/group). Ordinate values in mEq per liter.

compared to the control group (Table 2). The recovery rise in the 30 percent group was significantly less pronounced, i.e., in terms of slope, than that observed in the 50 percent group; hence a significant group X time interaction emerged when the two hemorrhage groups were compared statistically (Table 2).

Arterial Base Excess: The direction, magnitude, and statistical significance of the alterations in base excess concentration were remarkably similar to those recorded for bicarbonate concentration (Figure 2). Statistically, the only major difference was a significant decrease (Table 3) in the base excess values of the control group between the beginning and end of the study period, i.e., from 7.1 $\pm$ 0.60 to 6.6 $\pm$ 0.52 mEq/l. The similarity in the magnitude of change of base excess and bicarbonate was readily evident immediately after 50 percent hemorrhage; mean bicarbonate concentration was reduced by 10.0 mEq/l, base excess by 9.4 mEq/l.

Interrelationships Among Measures: Table 4 summarizes the possible correlations between variables measured immediately after 30

and 50 percent blood loss. The correlation coefficients for data interrelationships at the end of the recovery period are summarized in Table 5. In both tables, data on mean arterial pressure ($\bar{P}_a$) and heart rate (HR), measured at the same time as the blood gas and acid-base variables and reported graphically in an earlier report (1), were included in the computations to determine the significance of correlations, if any, between hemodynamic and blood gas/acid-base variables. Base excess data were not included in tables since the significant interrelationships were essentially the same as those associated with bicarbonate.

Immediately after hemorrhage (Table 4), arterial pH showed a significant positive correlation to arterial P CO_2 and HCO_3^- concentration when all hemorrhaged animals were included in the calculations. Insofar as HCO_3^- concentration was concerned, the significance of this relationship persisted when the 30 and 50 percent hemorrhage groups were evaluated separately. Statistically significant correlations between these variables are, perhaps, not surprising since their interrelationships, as described by the Henderson-Hasselbalch equation, determines the acid-base status of the blood. At a constant P CO_2, for example, pH increases as bicarbonate concentration increases. In any event, the following least-squares linear regression equations describe these relationships for all hemorrhaged pigs:

(1) $pH = 7.380 + 0.0034\ P\ CO_2$, S.D. = 0.029.

(2) $pH = 7.367 + 0.0046\ [HCO_3^-]$, S.D. = 0.022.

All hemorrhaged animals as a single group showed arterial P O_2 to be negatively correlated with pH, P CO_2, $[HCO_3^-]$, and $\bar{P}_a$. Arterial $\bar{P}_a$ was positively correlated with P CO_2 and $[HCO_3^-]$. The following least squares linear regression equations applied to these relationships:

(3) $P\ O_2 = 1270 - 158\ pH$, S.D. = 8.61.

(4) $P\ O_2 = 139 - 1.43\ P\ CO_2$, S.D. = 2.90.

(5) $P\ O_2 = 125 - 1.35\ [HCO_3^-]$, S.D. = 5.91.

(6) $P\ O_2 = 116 - 0.41\ \bar{P}_a$, S.D. = 5.63.

(7) $\bar{P}_a = 21.7 + 2.49\ P\ CO_2$, S.D. = 15.0.

(8) $\bar{P}_a = 2.36\ [HCO_3^-]$, S.D. = 17.6.

When computations were restricted to the individual hemorrhage groups, only the negative correlation between arterial P O_2 and P CO_2 retained statistical significance, probably because of the limited number of degrees of freedom associated with the collected data.

At the end of the recovery period, all hemorrhaged pigs considered, arterial pH was positively correlated to $[HCO_3^-]$ and negatively correlated to P O_2 (Table 5). Arterial P O_2 was negatively correlated to $[HCO_3^-]$. Finally, HR was positively correlated with P CO_2 and negatively correlated with $\bar{P}_a$. The following least squares linear regression equations were obtained for these relationships:

(9) $pH = 7.222 + 0.0743\ [HCO_3^-]$, S.D. = 0.0134.

(10) $pH = 0.0046\ P\ O_2$, S.D. = 0.0101.

(11) $P\ O_2 = 131 - 1.59\ [HCO_3^-]$, S.D. = 2.60

(12) $HR = -384 + 11.96\ P\ CO_2$, S.D. = 10.85.

(13) $HR = 203 - 0.89\ \bar{P}_a$, S.D. = 12.2.

Most of the foregoing correlations remained statistically significant when the computations were restricted to the individual hemorrhage groups. The only additional information revealed by these computations was a significant, but barely so, negative correlation between $\bar{P}_a$ and P CO_2 in the 50 percent hemorrhage group.

DISCUSSION

Control Observations: The control data obtained in this study show that the blood gas and acid-base characteristics of young domestic swine differ in several important respects from those reported for humans and dogs. The normal pH of porcine arterial blood averages about 7.50, a value that is distinctly higher than the 7.40 usually reported for humans (60) or dogs (61) studied under equivalent experimental conditions. Arterial P CO_2 values of pig blood show an average value of about 40 torr, the same as humans (60) but higher than the 33 or 34 torr reported for dogs (61). The high arterial pH value in pigs is attributable to an elevated bicarbonate concentration, averaging about 30 mEq/l as compared to 25 mEq/l in humans (61) and 22 mEq/l in dogs (33). In addition, the normal base excess of swine is about +7 mEq/l as compared to 0 in both humans and dogs (62,63). The elevated base excess and pH values seen in swine are attributable for the most part to high bicarbonate concentrations relative to those characteristic of humans or dogs. Porcine data consistent with this interpretation have been reported by Scott and McIntosh (62). This interpretation, nevertheless, should be tempered because the base excess values reported in this study, as well as the study of Scott and McIntosh (62), were based on the Siggaard-Anderson nomogram for human blood (63) which assumes a normal P CO_2 of 40 torr and a pH of 7.40 in estimating base excess or base deficit concentration. Scott and McIntosh (62) constructed a nomogram for pig blood, assuming a normal pH of 7.40, and found it in good agreement with Siggaard-Anderson's

nomogram (63). A divergent opinion concerning the comparability of porcine and human nomograms was reported in an abstract by Riordan et al (64). Base excess computations for swine, obviously, should be based on the acid-base characteristics of a normal porcine population, i.e., at a pH of 7.50 and a P CO_2 of 40 torr, base excess by definition would be zero. Finally, the normal arterial P O_2 of pigs ranges from about 77 to 83 torr, compared to the 82-90 torr usually seen in dogs (61) and 85-95 torr usually seen in humans (60). Swine, it might be noted, also exhibit lower arterial oxygen saturation values because their hemoglobin-oxygen dissociation curve is displaced to the right relative to that of dogs and humans (65).

Hemorrhage Effects: Immediately after hemorrhage, only pigs losing 50 percent of their estimated blood volume showed significant alterations in blood gas and acid-base status. Metabolic acidosis was readily apparent in these animals. It was equally apparent, in view of the small changes in arterial pH that were recorded, that conscious, unrestrained young pigs can readily and effectively compensate for the acid load evoked by severe blood loss. Metabolic acidosis was evidenced by the markedly reduced base excess values that were recorded immediately after hemorrhage. Inadequate arterial oxygen transport and, as a consequence, increased production of lactic acid appears to be the responsible mechanism. Accordingly, these same pigs showed an increase in arterial concentration of lactic acid that was nearly equivalent in magnitude to the change in base excess concentration (unpublished data). Lactacidemia, in addition, appears to be responsible for the reduction in arterial bicarbonate concentration, a key compensatory mechanism in ameliorating the effects of acid loads. Additionally, lactacidemia appears to be responsible, at least indirectly, for the reduction in arterial P CO_2 and the increase in arterial P O_2 which were observed immediately after the hemorrhage episode. At this time, P CO_2 was negatively correlated with P O_2, presumably as a result of lactacidemia and a consequent increase in ventilation. Chemoreceptor drive, at least in terms of arterial P CO_2, did not seem responsible for post-hemorrhage hyperventilation, for if this were so one would have expected a positive correlation between arterial P CO_2 and P O_2. Such an interpretation would not rule out the alternative possibility that local P CO_2 levels, or for that matter local pH or P O_2 levels, in the central nervous system were regulating ventilation. In fact, in light of the data reported here and evidence of a decrease in cerebral blood flow during severe hemorrhagic hypotension in rats (66), dogs (67,68), monkeys (69,70), and man (71) (but so far not in pigs), the alternative interpretation seems likely. It is pertinent, perhaps, that similar central mediation of ventilatory control was proposed nearly 60 years ago by Gesell (72) to account for hyperpnea which was so often observed in the absence of arterial acidosis, hypercapnia, or hypoxia. Skillman, et al (73) expressed the opinion that epinephrine release in response to hypotension also played a role in the hyperventilation observed after hemorrhage in human subjects.

In an earlier report on these pigs (1), we showed that heart rate was unaltered, and in some instances reduced, immediately after hemorrhage. Here we found no significant correlation between heart rate and mean arterial pressure. Taken together, these observations indicate that normal baroreceptor functions become inoperative in swine sometime during the course of blood loss. The mechanisms underlying this apparent abnormality are unknown.

When all hemorrhaged pigs are evaluated as a group, mean arterial pressure showed a significant positive correlation to both arterial P CO_2 and bicarbonate concentration. A significant negative correlation between mean arterial pressure and P O_2 was observed also. In simple terms, these interrelationships indicated that the greater the post-hemorrhage decrement in arterial pressure the greater the decrements in P CO_2 and bicarbonate concentration and the greater the increment in P O_2.

In general, the immediate post-hemorrhage results and interpretations obtained in the present study are consistent with the rather limited acid-base data collected by others from swine subjected to hemorrhagic hypotension. Most reported investigations, as indicated earlier, were conducted with anesthetized animals, utilized a Wiggers or other fixed hypotension procedure for inducing shock and, in many instances, included mechanical control of pulmonary gas exchange. Data obtained in such studies, consequently, cannot be compared in any meaningful way to the data reported here. In fact, the scientific literature contains only one report, at least insofar as we are aware, in which the acid-base status of conscious swine was evaluated following a fixed-volume hemorrhagic hypotension. This study, which will be discussed below, was conducted by Buell (74).

Spontaneous Recovery: With one exception, the blood gas and acid-base changes associated with 50 percent loss of the estimated blood volume reverted spontaneously to control levels over the first two or three hours of recovery. Arterial P O_2 showed a more delayed recovery, reaching control levels after five hours. Again with the exception of arterial P O_2, the early stages of spontaneous recovery in pigs subjected to 30 percent blood loss were characterized by progressive reversion of blood gas and acid-base values toward control levels. During the latter stages of spontaneous recovery, however, the values recorded for these animals exceeded not only their own prehemorrhage control levels, but the levels recorded in untreated control pigs as well. Arterial P O_2 following 30 percent hemorrhage, in contrast, showed a progressive decline over the course of the recovery period, a response that appeared identical to that recorded in control animals. The elevated acid-base values, relative to control values, seen during the latter stages of the recovery were not limited to pigs subjected to 30 percent blood loss. Significantly elevated acid-base values were observed also in pigs subjected to 50 percent blood loss. The factors responsible for these effects are unknown, but

the results suggest a resetting of the set-point for acid-base regulation in the recovered animal. Similar observations, to the best of our knowledge, have not been reported in recent literature, perhaps because so little effort has been directed to the functional changes associated with spontaneous recovery in the conscious animal. In the older literature, one of first definitive studies of post-hemorrhage recovery of acid-base status was reported by Buell (74) in 1919. She showed in large conscious swine, of all things, that the post-hemorrhage alkali reserve (bicarbonate) reverted to and in some instances exceeded control levels as spontaneous recovery progressed. Similar results were reported by Tatum (15) in 1920 for conscious rabbits and by Bennett in 1927 (19) for conscious dogs.

In part at least, recovery in animals subjected to 50 percent blood loss would seem attributable to an improvement in arterial oxygen transport and a consequent amelioration of the anaerobic conditions in the tissues which led to lactacidemia and bicarbonate buffer depletion. In support of this contention, it was shown in an earlier report (1) that post-hemorrhage expansion of plasma volume, attributable to fluid transfer from the extra- to the intravascular space, could replenish about half of the blood lost during hemorrhage. In addition, a progressive increase in heart rate, and presumably cardiac output, was observed also.

Similar tachycardia and plasma volume expansion, but of lesser magnitude, were seen also in the pigs subjected to 30 percent blood loss (1). In these animals, however, the compensatory responses that occurred during and immediately after hemorrhage were highly effective in preventing the acid-base alterations characteristic of pigs subjected to more severe hemorrhage. Mild lactacidosis (unpublished data) was observed in these pigs but, as is readily evident in the data recorded here, precise adjustments in bicarbonate production and pulmonary carbon dioxide elimination effectively maintained the normal blood gas and acid-base status of arterial blood.

At the end of the recovery period, linear regression analyses of blood gas and acid-base data showed a highly significant negative correlation between arterial $P O_2$ and both pH and bicarbonate concentration, but no significant relationship between $P O_2$ and $P CO_2$. Thus, ventilatory drive appeared to be operating in a manner equivalent to that observed immediately after hemorrhage. Heart rate at this time point in the study was negatively correlated with arterial pressure; i.e., the lower the arterial pressure the higher the heart rate. This relationship might be expected if normal baroreceptor functions were re-established during the course of spontaneous recovery.

CONCLUSIONS

- When measured under recumbant, unrestrained, resting condition, the arterial pH, P CO_2, [HCO_3^-], and base excess values of the conscious young domestic pig exceed those usually seen in humans. The arterial P O_2 of the pig is lower than that of humans.

- Hemorrhage amounting to 30 percent of the estimated blood volume has no apparent effect on the arterial blood gas and acid-base status of the conscious pig. Increased bicarbonate production and increased pulmonary carbon dioxide elimination would appear to be the primary mechanisms compensating for a hemorrhage-induced increase in lactic acid production.

- Hemorrhage amounting to 50 percent of the estimated blood volume leads to a metabolic acidosis, largely compensated by bicarbonate buffering of the lactic acid produced during hemorrhagic hypotension. An increase in pulmonary ventilation eliminates the carbon dioxide so produced.

- Spontaneous recovery from hemorrhagic hypotension in pigs subjected to 50 percent blood loss is manifested by a return of all acid-base values to control levels within 2 to 4 hours. Thereafter the values exceed control levels. Spontaneous recovery in pigs subjected to 30 percent blood loss is manifested by a similar rise of acid-base variables, but not P O_2, above control levels. Recovery from both 30 and 50 percent blood loss appears to entail compensatory replenishment of plasma volume and tachycardia, hence an improvement of tissue oxygen delivery.

- During hemorrhage and spontaneous recovery therefrom, normal chemoreceptor drive of ventilation appears blunted, if not eliminated. Baroreceptor drive of heart rate is blunted or eliminated immediately after hemorrhage but returns as spontaneous recovery proceeds.

RECOMMENDATIONS

- The alterations in blood metabolite and electrolyte concentrations associated with hemorrhagic hypotension and spontaneous recovery therefrom need to be documented for conscious swine.

- Plasma protein changes and their role in the replenishment of plasma volume during and after hemorrhage in swine need to be quantitated.

- The role of the spleen, if any, in compensating for reduced arterial oxygen transport in the conscious hemorrhaged pig should be evaluated.

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LEGENDS OF TABLES

Table 1 Two-Factor Analysis of Variance Summary: 3 Group

Table 2 Two-Factor Analysis of Variance Summary: Group Pairs

Table 3 Single Factor Analysis of Variance Summary: Time

Table 4 Correlation Matrix: pH, P CO_2, [HCO_3^-], Mean Arterial Pressure ($\bar{P}_a$), and Heart Rate (HR) Immediately after 30 and 50 Percent Hemorrhage of the Estimated Blood Volume

Table 5 Correlation Matrix: pH, P CO_2, HCO_3^-, P O_2, Mean Arterial Pressure ($\bar{P}_a$), and Heart Rate (HR) after 5 Hours Spontaneous Recovery from Hemorrhagic Hypotension

APPENDIX

Table 1. Two-Factor Analysis of Variance Summary: 3 Group

Measurement	Group	F-Ratio Time	G x T
pH	1.35	3.56*	2.91
P CO_2	6.36*	18.88*	14.21*
P O_2	20.34*	17.54*	9.36*
$[HCO_3^-]$	6.01*	14.01*	10.27*
Base Excess	5.61*	13.47*	10.02*

*Indicates significant effect ($P \leq 0.05$): 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

Measurement	Pair	F-Ratio Group	F-Ratio Time	F-Ratio G x T
pH	C x 30	0.06	0.97	2.24*
	C x 50	2.77	2.98*	4.10*
	30 x 50	1.69	4.49*	2.16*
$P CO_2$	C x 30	2.64	1.78	3.69*
	C x 50	3.26	17.03*	18.27*
	30 x 50	14.81*	21.69*	13.06*
$P O_2$	C x 30	0.14	6.23*	0.99
	C x 50	46.59*	16.59*	14.69*
	30 x 50	25.73*	17.46*	8.87
$[HCO_3^-]$	C x 30	3.96	2.81*	8.70*
	C x 50	2.52	10.38*	13.15*
	30 x 50	11.86*	16.42*	7.65*
Base Excess	C x 30	2.94	2.45*	8.45*
	C x 50	3.09	10.16*	13.09*
	30 x 50	9.92*	15.77*	7.33*

*Indicates significant effect ($P \leq 0.05$) Group, $F_{1,10}=4.96$; Time, $F_{7,70}=2.14$; G x T, $F_{7,70}=2.14$. C refers to control group, 30 and 50 to the 30 and 50 percent hemorrhage groups, respectively.

Table 3. Single Factor Analysis of Variance Summary: Time

Measurement	Group	F-Ratio
pH	Control	1.24
	30% Hemorrhage	1.75
	50% Hemorrhage	3.85*
$P\ CO_2$	Control	1.67
	30% Hemorrhage	3.55*
	50% Hemorrhage	19.79*
$P\ O_2$	Control	5.39*
	30% Hemorrhage	2.54*
	50% Hemorrhage	18.09
$[HCO_3^-]$	Control	1.95
	30% Hemorrhage	8.41*
	50% Hemorrhage	12.35*
Base Excess	Control	2.36*
	30% Hemorrhage	2.36*
	50% Hemorrhage	6.80*

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

Table 4. Correlation Matrix: pH, P CO_2, $[HCO_3^-]$, Mean Arterial Pressure ($\bar{P}_a$), and Heart Rate (HR) Immediately after 30 and 50 Percent Hemorrhage of the Estimated Blood Volume.

	pH	P CO_2	$[HCO_3^-]$	P O_2	$\bar{P}_a$
		All Hemorrhaged Pigs (df=10)			
P CO_2	0.59*				
$[HCO_3^-]$	0.79*	0.88*			
P O_2	-0.55*	-0.96*	-0.82*		
$\bar{P}_a$	0.42	0.76*	0.64*	-0.86*	
HR	0.39	-0.10	-0.38	0.11	-0.15
		30 Percent Hemorrhage (df=4)			
P CO_2	-0.66				
$[HCO_3^-]$	0.80*	-0.15			
P O_2	0.23	-0.91*	-0.05		
$\bar{P}_a$	-0.05	0.32	0.13	-0.15	
HR	-0.21	-0.19	-0.63	0.33	-0.57
		50 Percent Hemorrhage (df=4)			
P CO_2	0.65				
$[HCO_3^-]$	0.83*	0.73*			
P O_2	-0.41	-0.78*	-0.52		
$\bar{P}_a$	-0.26	0.32	-0.01	-0.63	
HR	-0.32	0.09	-0.43	-0.15	0.57

*$p<0.05$: df=10; r=0.497; df=4, r=0.729.

Table 5. Correlation Matrix: pH, P CO_2, HCO_3^-, P O_2, Mean Arterial Pressure ($\bar{P}_a$), and Heart Rate (HR) after 5 Hours Spontaneous Recovery from Hemorrhagic Hypotension.

	pH	P CO_2	$[HCO_3^-]$	P O_2	$\bar{P}_a$
		All Hemorrhaged Pigs (df=10)			
P CO_2	0.42*				
$[HCO_3^-]$	0.74*	0.42			
P O_2	-0.87*	0.03	-0.72*		
$\bar{P}_a$	0.11	-0.34	-0.18	-0.21	
HR	-0.30	0.81*	0.17	0.23	0.88*
		30 Percent Hemorrhage (df=4)			
P CO_2	-0.34				
$[HCO_3^-]$	0.72	0.28			
P O_2	-0.83*	0.04	-0.79*		
$\bar{P}_a$	-0.33	0.18	-0.51	-0.04	
HR	-0.33	0.96*	0.26	0.17	0.05
		50 Percent Hemorrhage (df=4)			
P CO_2	-0.21				
$[HCO_3^-]$	0.86*	0.66			
P O_2	-0.74*	-0.23*	-0.73*		
$\bar{P}_a$	0.27	-0.75*	-0.14	-0.41	
HR	-0.05	0.92*	0.33	0.02	-0.81*

$P \leq 0.05$: df=10, r=0.497; df=4, r=0.729

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