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Resuscitation of Conscious Pigs Following Hemorrhage: Blood Gas and Acid-Base Status During Fixed Volume Hemorrhage and Resuscitation with Hypertonic Saline/Dextran

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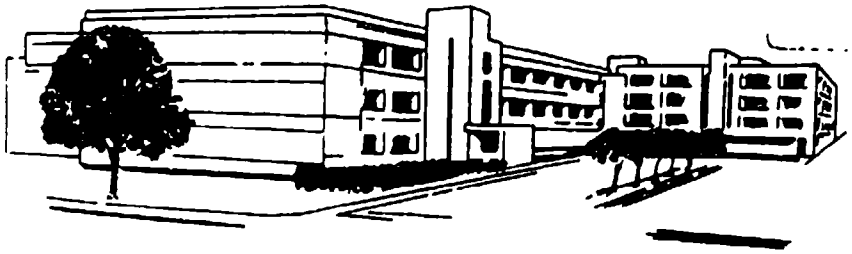

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Resuscitation of Conscious Pigs Following Hemorrhage: Blood Gas and Acid-Base Status During Fixed Volume Hemorrhage and Resuscitation with Hypertonic Saline/Dextran, et al

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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Six conscious, chronically-instrumented pigs were subjected to a progressive, fixed-volume hemorrhage (37.5 ml/kg over 1 h) and subsequent resuscitation with 7.5% NaCl/6% Dextran 70 (4ml/kg). Hemorrhage led to increases in arterial PO_2, HbO_2, plasma lactate, base deficit, and mixed venous PCO_2. It led to decreases in arterial PCO_2, plasma bicarbonate, buffer base, and mixed venous PO_2, HbO_2, and pH. These effects were attributable to reduced O_2 delivery, lactacidemia, hyperventilation and hemodilution. Resuscitation with hypertonic saline/dextran produced an immediate increase in arterial PCO_2 and base deficit, and a decrease in pH. These effects were attributable to an increase in cardiac output and a transfer of venous blood attributes to the arterial circulation. Resuscitation also produced an immediate decrease in arterial buffer base, an effect attributable to hemodilution. Subsequently, over 4 h, most variables gradually reverted toward control levels, thereby rectifying the deleterious blood gas and acid-base disturbances produced by severe hemorrhage.

Keywords: Hemorrhage; Partial Pressure, Carbon dioxide, Oxygen; Oxyhemoglobin; Sodium Chloride; Dextran

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ABSTRACT

Six conscious, chronically-instrumented pigs were subjected to a progressive, fixed-volume hemorrhage (37.5 ml/kg over 1 h) and subsequent resuscitation with 7.5% NaCl/6% Dextran 70 (4 ml/kg). Hemorrhage led to increases in arterial PO_2, HbO_2, plasma lactate, base deficit, and mixed venous PCO_2. It led to decreases in arterial PCO_2, plasma bicarbonate and buffer base, as well as mixed venous PO_2, HbO_2 and pH. These effects were attributable to reduced O_2 delivery, lactacidemia, hyperventilation and hemodilution. Resuscitation with hypertonic saline/dextran produced an immediate increase in arterial PCO_2 and base deficit, and a decrease in pH. These effects were attributable to an increase in cardiac output and a transfer of venous blood attributes to the arterial circulation. Resuscitation also produced an immediate decrease in arterial buffer base, an effect attributable to hemodilution. Subsequently, over 4 h, most variables gradually reverted toward control levels, thereby rectifying the deleterious blood gas and acid-base disturbances produced by severe hemorrhage.

Key Words: swine, blood loss, lactacidemia, base deficit, buffer base, hypertonic saline/dextran

INTRODUCTION

Hemorrhage produces functional changes in conscious animals that may differ both qualitatively and quantitatively from those seen in anesthetized animals. Conscious pigs, for example, respond to severe blood loss with an increase in O_2 consumption, an effect that is largely attributable to an increase in muscle activity [1]. This behavioral compensation, which presumably enhances venous return and cardiac output during hypovolemia, is not seen in anesthetized animals. Conscious pigs also respond to blood loss with hyperventilation [1], an effect that is often absent, attenuated or prevented when ventilation is mechanically controlled in anesthetized animals. Hypovolemia leads to hemodilution and a reduced cardiac output with a resultant decrease in arterial O_2 delivery in both awake and anesthetized animals; however, the magnitude of these effects in conscious animals may differ substantially from those seen in anesthetized animals. Similarly, both awake and anesthetized animals exhibit lactacidemia following severe blood loss, but the extent of the response may be attenuated or exaggerated by differences in ventilation, muscle activity, tissue O_2 demand and arterial O_2 delivery [1].

Because of the foregoing differences and those reported elsewhere [2], we feel that conscious, chronically-instrumented animals are superior to chemically-restrained animals for studies of hemorrhagic hypotension. A conscious animal model can offset the dysfunctions associated with hemorrhage by mobilizing a range of compensatory responses that may be unavailable or significantly altered in models involving chemical restraint. Furthermore, the conscious model would seem to have greater clinical relevancy since one rarely sees severe blood loss in anesthetized accident victims or combat casualties. Use of a conscious animal model, however, poses a number of problems, not the least of which is a lack of qualitative and quantitative data on the dysfunctions associated with hemorrhage and the compensatory responses that are consequently elicited. Too few studies have employed conscious animals. In the study reported here, we addressed this problem using a conscious, chronically-instrumented porcine model to investigate the blood gas and acid-base changes produced by a potentially lethal fixed-volume hemorrhage. The study was a component of a more comprehensive investigation that compared the resuscitative effectiveness of 0.9% NaCl, 7.5% NaCl, 6% Dextran 70, and 7.5% NaCl/6% Dextran 70 [3]. We were specifically concerned with the following questions: Do the compensatory responses

normally mobilized by conscious animals effectively ameliorate the adverse blood gas and acid-base effects usually associated with hemorrhage? To what extent during hemorrhage are various components of the blood buffer system altered by lactacidemia and transcapillary refill? Finally, does resuscitation with 7.5% NaCl/6% dextran produce significant changes in the blood gas and acid-base status of hypovolemic animals?

MATERIALS AND METHODS

The procedures used to prepare the pigs for study and the experimental conditions associated with hemorrhage and subsequent resuscitation with hypertonic saline/dextran are described in previous reports [1,3]. Briefly, 7 to 10 days before study immature domestic swine (n=6) were chronically instrumented with carotid and pulmonary artery catheters. At the same time, a splenectomy was performed and a sideport catheter [4] was chronically implanted in the aorta distal to the kidneys. Over a 3 day period before surgery and recommencing 2 days thereafter, the pigs were trained 60 min daily to accept a respiratory mask and physical restraint in a Pavlov sling.

On the day of study, each pig was brought into the laboratory and placed in the sling with the mask secured over the snout; the mask was used to record ventilatory and metabolic variables as reported elsewhere [1]. The carotid and pulmonary artery catheters were connected by pressure-injection lines to 3-way stopcocks and pressure transducers for measurements of hemodynamic and O_2 delivery variables [1,3], and for sample removal to determine blood gas and acid-base status. The sideport catheter also was connected to a 3-way stopcock to allow blood removal during the hemorrhage phase of the study. Stagnant blood and heparinized saline were cleared from all 3 catheters and they were refilled with fresh heparinized saline (100 units/ml). The animal was allowed to remain quietly in the sling until minimal O_2 consumption values were achieved and maintained for at least 10 min. This rest interval ranged from 30 to 60 minutes. Control measurements were taken in triplicate at 10-min intervals, and hemorrhage was initiated immediatel thereafter. Blood was progressively removed from the animal on an exponential scale over a 60 min period to achieve a total hemorrhage volume of 37.5 ml/kg. Blood samples were taken from the carotid and pulmonary arteries at 9, 19, 31.5, 44 and 60 min (i.e., after successive 7.5 ml/kg increments of blood loss) for measurements of blood gas and acid-base status. Immediately after hemorrhage, the pig was given a 4

ml/kg bolus injection of 7.5% NaCl/6% Dextran 70 into the pulmonary artery, and additional blood samples were taken at 5, 15, 30, 60, 180, and 240 min of the subsequent recovery period. Sample volumes removed during the control and hemorrhage phases of the study were included in the hemorrhage volume.

Blood gas and acid-base measurements were made at 38.5°C immediately after sample removal using an Instrumentation Laboratory Model 1303 blood gas analyzer and Model 282 Cooximeter (Instrumentation Laboratory Inc., Lexington, MA). Both instruments were calibrated and maintained according to the manufacturer specifications. Plasma lactate concentration was measured enzymatically using a GEMSAEC autoanalyzer (Electronucleonics, Inc., Fairfield, NJ) and Sigmasystem test kits (Sigma Chemical Co., St Louis, MO), and plasma protein concentration was determined colorimetrically using a Bio-Rad protein assay (Bio-Rad Laboratories, Richmond, CA). Plasma protein anion concentration was calculated by the Van Slyke equation [5]:

$$\text{Protein Anion (mEq/L)} = 0.104(\text{g protein/L})(pH_s - 5.08)$$

Buffer base concentration and changes in base deficit were estimated by nomograms specific for pig blood [6]. These nomogram values were corrected for losses of plasma protein anion during and subsequent to hemorrhage.

Data were evaluated by single-factor, repeated-measures, analyses of variance with $P \leq 0.05$ being selected as indicative of significant differences. These analyses were applied first to the hemorrhage period and then to the first hour of recovery, i.e. before any animals had died. In addition, mean $\pm$ SEM values were calculated for each time point during the control, hemorrhage and recovery periods. At one hour and thereafter during the recovery period, two mean values were calculated for the time point that preceded death of an animal: one mean included and the other excluded the nonsurviving animal. This double calculation was directed at minimizing data distortion that might result from changes in interanimal variance associated with a reduction in group size. Representative SEM values are indicated in the figures that follow.

RESULTS

Responses to hemorrhage in animals described here were not significantly different from those seen in the other groups

included in the overall investigation [3]. Subsequent to hemorrhage most animals in the other groups died, hence statistical constraints precluded between-group comparisons during the recovery period. In general, death was preceded by progressively more pronounced hypoventilation, lacacidemia, and hypometabolism. Of the six pigs receiving 7.5% NaCl/6% Dextran 70, four survived and two died, one at 70 min and the other at 190 min after resuscitation. The overall investigation did not include a non-hemorrhaged control group because previous studies [7,8] with equivalently instrumented swine models have shown that none of the measured functional variables were appreciably altered as function of time alone (up to 6 h).

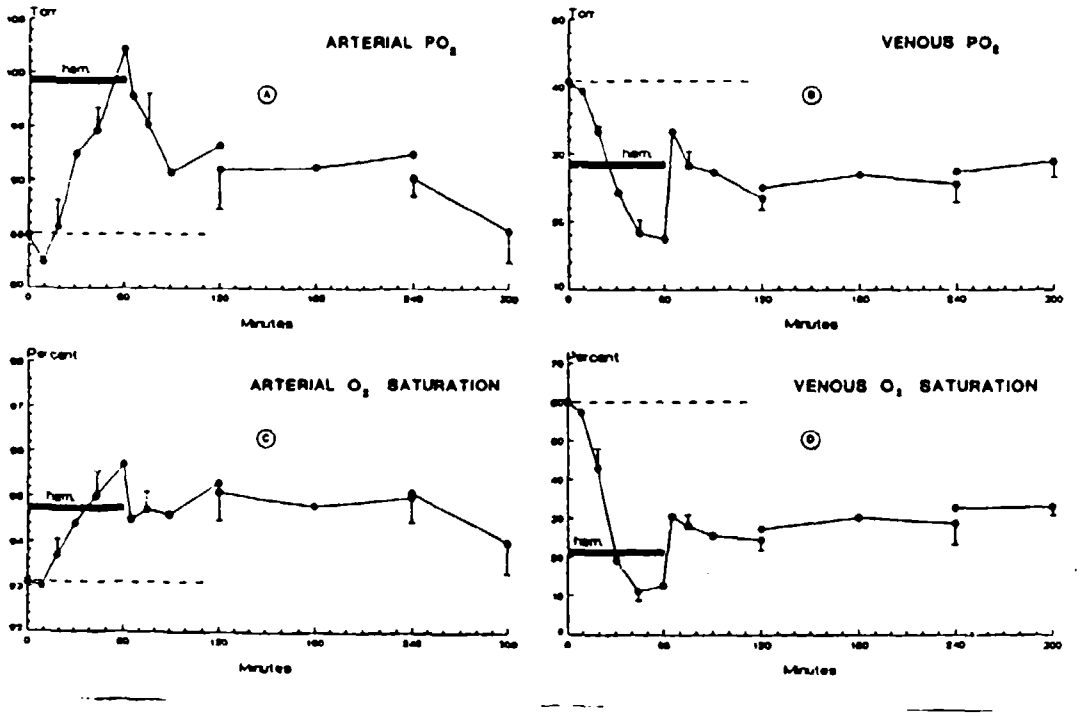

Figure 1. Effects of progressive fixed-volume hemorrhage (37.5 ml/kg) followed by resuscitation with 7.5% NaCl/6% dextran on arterial and mixed venous blood oxygenation. Resuscitation (4 ml/kg) was provided immediately (over 1 min) after hemorrhage. Breaks in the plots indicate time points at which mean and S.E.M. values were calculated to include as well as exclude an animal that died shortly thereafter. Solid bar depicts hemorrhage interval, dashed line control level for each variable.

A progressive and significant increase in arterial PO_2, from 85±1.4 to 102±3.0 torr, was observed over the course of the hemorrhage episode (Fig. 1A). Mixed venous PO_2, in contrast, decreased significantly during hemorrhage, from 41±1.3 to 17±2.1 torr (Fig. 1B). Opposite effects also were seen following resuscitation with hypertonic saline/dextran. At the 5-min point following treatment, arterial PO_2 was reduced by 4.5 torr while mixed venous PO_2 was increased by 16 torr. These effects of hypertonic saline/dextran, though statistically significant overall, were not sustained on the venous side of the circulation during the remainder of the recovery period. Rather, they regressed to levels intermediate to those recorded before and immediately after hemorrhage. Arterial PO_2 gradually returned toward control levels as recovery progressed.

The effects of hemorrhage and hypertonic saline/dextran resuscitation on arterial (Fig. 1C) and mixed venous (Fig. 1D) oxygen saturation were consistent with expectations. The values rose and fell significantly in accordance with changes in PO_2. Again, resuscitation had a more pronounced effect on the venous side, the HbO_2 values rising from 12.6±2.47% at the end of hemorrhage to 30.5±5.27% at 5 min into the recovery period. Impending death of animals during the recovery period, one at 130 and the other at 250 min into the overall experiment, had a tendency to distort mean and SEM values for both PO_2 and HbO_2. At the 120 min point, for example, the pig that subsequently died had an arterial PO_2 value that was 11 torr higher than the mean for the remainder of the group.

Hemorrhage caused a significant, progressive decrease in arterial PCO_2, from 42±1.0 to 28±2.9 torr, and a progressive increase in mixed venous PCO_2, from 49±0.9 to 58±2.5 torr (Figs. 2A, 2B). The bolus of 7.5% NaCl/6% dextran produced an abrupt and significant reversal of both changes, arterial PCO_2 rising to 36±1.7 torr and mixed venous PCO_2 decreasing to 51±1.8 torr at 5 min into the recovery period. Subsequent arterial values rose slowly toward, but did not reach, prehemorrhage control levels. Subsequent venous values were actually lower than control levels.

Despite the marked reduction in arterial PCO_2 during hemorrhage, arterial pH was not altered significantly (Fig. 2C). Mixed venous pH, however, showed a significant, progressive decline from 7.39±0.011 to 7.19±0.022 (Fig. 2D). Resuscitation with hypertonic saline/dextran had an immediate effect on arterial but not on venous pH. At 5 min into the recovery period, arterial pH was reduced from a

post-hemorrhage level of 7.41±0.044 to 7.25±0.021 while venous pH remained essentially unchanged. Thereafter, both arterial and venous pH values reverted toward control levels. Impending death was associated with a tendency for lowered arterial and venous PCO_2 values. This tendency was particularly evident in arterial blood measurements made at 240 min into the overall experimental period; the nonsurviving animal had a PCO_2 value that was 7 torr below the mean for the surviving animals.

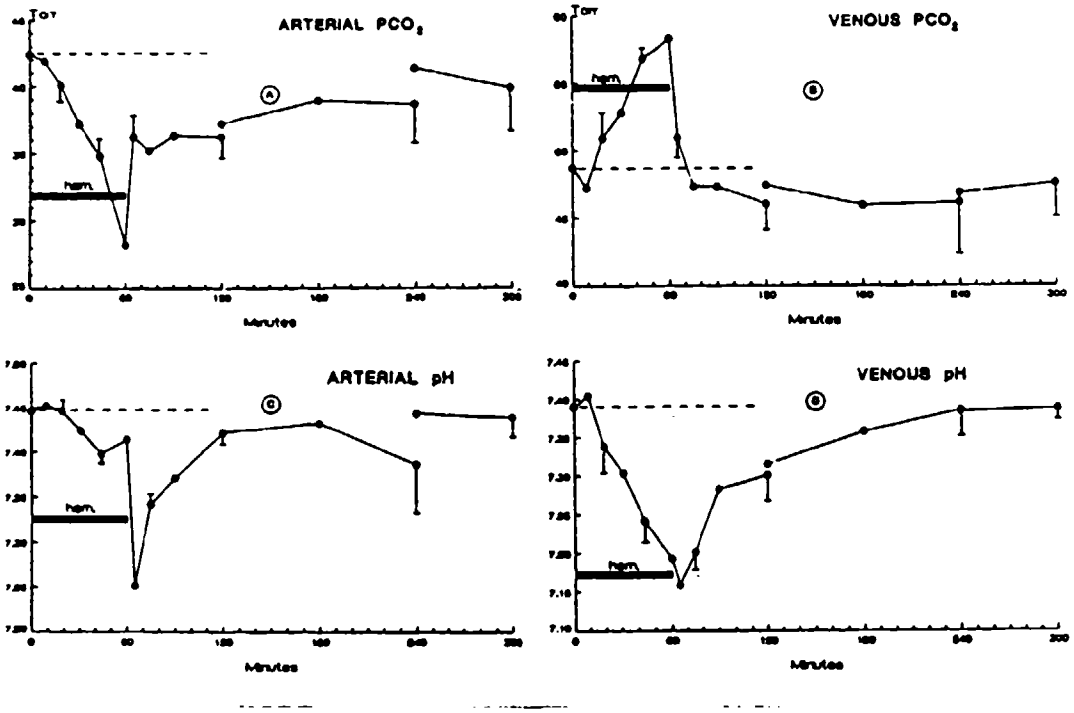

Figure 2. Effects of progressive fixed volume hemorrhage followed by resuscitation with hypertonic saline/dextran on the pH and PCO_2 of arterial and mixed venous blood. See Fig. 1 for details.

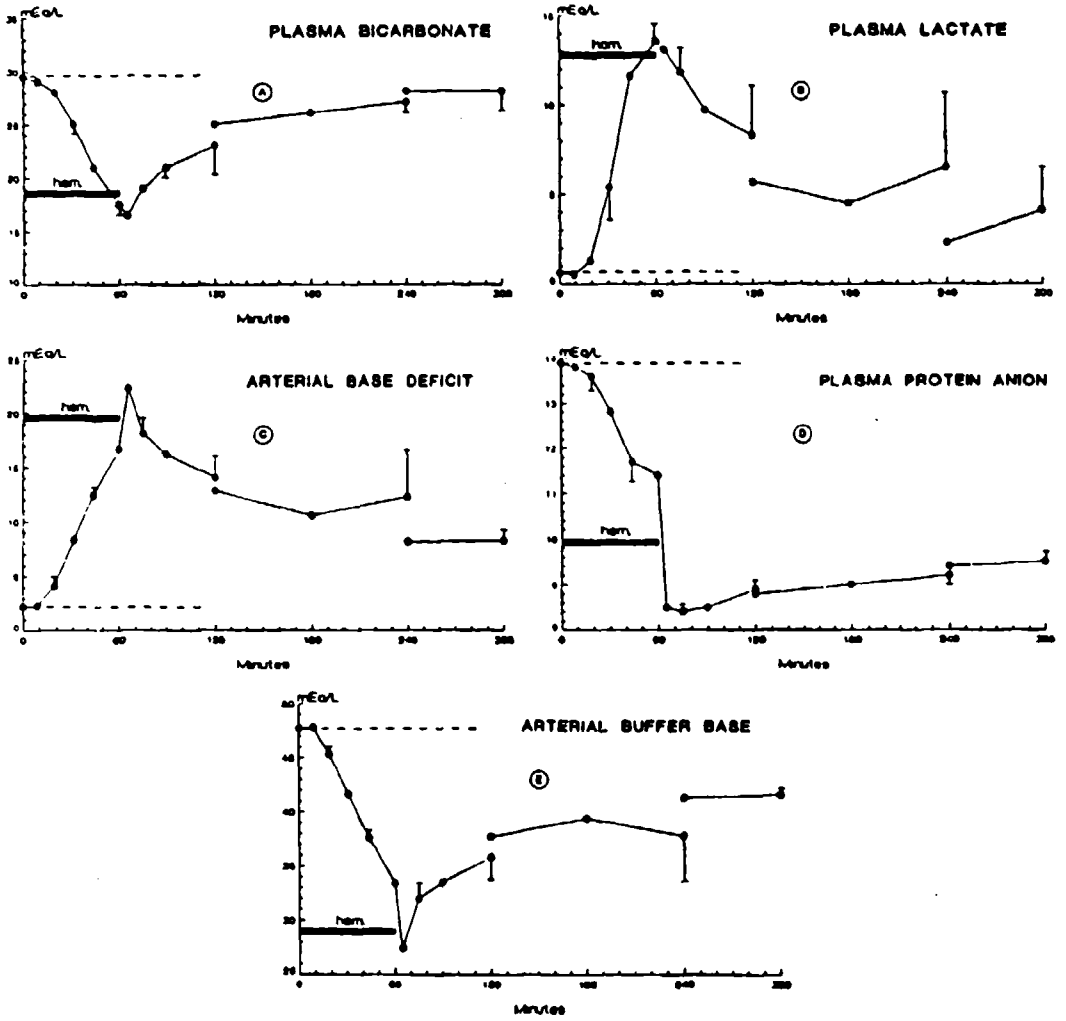

Figure 3. Effects of progressive fixed volume hemorrhage followed by resuscitation with hypertonic saline/dextran on plasma bicarbonate, lactate and protein anion concentrations and on base deficit and buffer base concentrations of arterial blood. See Fig. 1 for details.

A significant, progressive reduction in the concentration of bicarbonate in arterial plasma was recorded during hemorrhage (Fig. 3A), an effect that was associated with concomitant and nearly equivalent increments in plasma lactate concentration (Fig. 3B). Accordingly, bicarbonate was reduced from 29.5±0.73 to 17.5±0.94 mEq/L, a change of 12 mEq/L, while lactate increased from 0.6±0.04 to 13.6±1.03

mEq/L, a change of 13 mEq/L. The bolus of 7.5% NaCl/6% dextran had little immediate effect on plasma bicarbonate or lactate concentrations, but over the course of recovery both variables gradually and significantly reverted toward prehemorrhage control levels.

Arterial base deficit (Fig. 3C) increased significantly, by 14.4±0.67 mEq/L, over the course of hemorrhage, a change that was about 2.4 mEq/L greater than the decrease in plasma bicarbonate concentration. Treatment with hypertonic saline/dextran led to an immediate further increase in arterial base deficit (of 4.6±0.58 mEq/L), but thereafter the values gradually returned toward control levels. Again, nonsurviving animals tended to distort mean and SEM values during recovery.

The concentration of plasma protein anion decreased progressively and significantly during hemorrhage, from 13.9±0.33 to 11.4±0.38 mEq/L (Fig. 3C). Following treatment with hypertonic saline/dextran, a sharp additional decrease (to 9.7±0.19 mEq/L) was recorded at 5 min into the recovery period. Subsequently, the values rose gradually but significantly as the recovery period was extended to 4 h.

Arterial buffer base also showed a significant progressive decrease during hemorrhage, from 47.7± 0.64 to 33.4±0.84 mEq/L. At the 5-min point following treatment with 7.5% NaCl/6% dextran, a further decrease to 27.1±1.42 mEq/L was recorded. At this time point, therefore, the buffering capacity of the arterial blood was reduced to approximately 57% of the control level. Over the remainder of the recovery period, buffer base values gradually recovered, reaching about 86% of the control level at the 4-hr point.

DISCUSSION

Hemorrhage Effects: As reported previously for these same pigs [1], hemorrhage caused a modest rise in O_2 consumption, a reduction in cardiac output and arterial O_2 delivery, marked metabolic acidosis, hemodilution and hyperventilation, effects that increased in magnitude as hemorrhage progressed. In large measure, these functional changes were responsible for the blood gas and acid-base changes recorded here. Hyperventilation, for example, caused the increase in arterial oxygen tension and saturation seen in the present study and reported by others [9,10]. Increased tissue O_2 extraction from perfusing blood was responsible for the decrements in mixed venous PO_2 and O_2 saturation recorded here. Lactacidemia

was responsible for the increase in mixed venous PCO_2 as well as the decreases in plasma bicarbonate and mixed venous pH. The unchanged arterial pH attested to the compensatory effectiveness of hyperventilation during hemorrhage.

Bicarbonate loss was a major contributor to the reduced blood buffer base and the elevated base deficit concentrations associated with severe hemorrhage. Perhaps not so readily apparent were the buffer changes attributable to decrements in hemoglobin and plasma protein concentration. In the present study, the contribution of hemoglobin to blood buffering capacity was automatically taken into account since porcine alignment nomograms were used to estimate buffer base and base deficit concentrations [6]; these nomograms incorporated corrections for changes in hemoglobin concentration. Under the conditions of the present study, hemoglobin loss during hemorrhage was responsible for only a small portion of the decrease in blood buffering capacity, about 1 mEq/L. These nomograms, however, like those for human blood, did not provide corrections for changes in plasma protein concentration. Their construction was based on an average population value for protein concentration [6], a value that was appropriate for our control measurements but was not appropriate for measurements made during hemorrhage. Transcapillary refill during hemorrhage [1] led to a progressive decrease in the concentration of plasma protein anion (2.5 mEq/L in the present study), and corrections had to be made for the resultant decrements in buffer base (see Methods).

Resuscitation Effects: Administration of hypertonic saline/dextran following hemorrhage produced both acute and chronic alterations in blood gas and acid-base status. Acutely, hypertonic saline/dextran led to a marked rise in mixed venous PO_2 and a modest decrease in arterial PO_2. It also produced an acute rise in arterial PCO_2 which in turn caused arterial pH to decrease sharply. The PCO_2 of mixed venous blood, on the other hand, was reduced almost to control levels. In terms of arterial blood at least, others have reported similar acute effects of hypertonic saline [11-15] and hypertonic saline/dextran [15] to hypovolemic animals.

Insofar as we are aware, only Velasco et al. [11] and Lopes et al. [13] have offered explanations for these acute effects. In both instances, the authors attributed the increase in arterial PCO_2 and decrease in pH (seen after hypertonic saline administration to anesthetized, hypovolemic dogs) to ventilatory suppression. They [11,13] stated that ventilatory rate was decreased but did not provide any

supporting data on either rate or minute volume. Results from our experiments suggest that ventilatory suppression is not the causative factor, at least not in conscious pigs; both expired and alveolar ventilation remained elevated during the acute stage of resuscitation [1]. A more plausible explanation is that hypertonic saline/dextran administration acutely causes a transfer of mixed-venous blood to the arterial circulation. Consistent with this interpretation are the directionally opposite changes in arterial and mixed venous PCO_2 (Figs. 2A,2B), a near equivalency of arterial and mixed-venous pH (Figs. 2C,2D), and the rapid increase in cardiac output with a resultant decrease in ventilation-perfusion ratio (V_A/Q_T) reported elsewhere [1]. Hypertonic saline, furthermore, causes vasodilation of the pulmonary vascular bed [14]. This interpretation necessarily implies that blood transit time in the pulmonary capillaries is too short to allow adequate diffusion of the elevated mixed-venous CO_2 load to the alveoli. However, if diffusion were a limiting factor, one might expect to see a sharp rise in the shunt fraction of pulmonary blood flow (Q_s/Q_T) shortly after administration of hypertonic saline/dextran; it rises only slightly [1].

A similar line of reasoning could account for the acute increase in venous PO_2, namely a transfer of arterial blood to the venous side of the systemic circulation. Decreased tissue O_2 demand [1], however, could also be a contributing factor.

In addition to changes in blood gas status, resuscitation with hypertonic saline/dextran induces a rapid transfer of water from the extra- to the intravascular space [3,14,15,17,18]. This transfer not only leads to a further reduction of blood hemoglobin level [1], but it also causes a further reduction of plasma protein level (Fig. 3D). Together, these resuscitation-induced changes lower buffer base concentration by approximately 6 mEq/L, a value that adds to the pre-existing, hemorrhage-induced decrement of 14.5 mEq/L to produce a total buffer base loss of 20.5 mEq/L. The effects of hemoglobin and plasma protein changes on blood-buffering capacity are seldom recognized in shock literature; clearly, the effects as seen here can be substantial.

Subsequent to the foregoing acute effects of hypertonic saline/dextran, some blood gas and acid-base variables rapidly reverted to control levels while others recovered slowly or not at all. At one extreme, venous PCO_2 reverted to, and remained at, prehemorrhage levels immediately after resuscitation. At the other extreme, venous PO_2 and saturation remained low, while buffer base and protein anion

concentrations increased only slightly over the 4 h recovery period. The gradual return of plasma bicarbonate toward control levels was particularly significant since it implied that resuscitation with hypertonic saline/dextran effectively restored normal renal function, at least in terms of replenishing body bicarbonate stores. In this respect, Maningas [19] showed that hypertonic saline/dextran administration caused a rapid increase in the renal blood flow of hypovolemic pigs.

For the most part, these chronic effects were associated with a gradual reversion of hemorrhage-induced changes in metabolic and cardiopulmonary dysfunctions toward control levels. Resolution of a disparity between O_2 delivery and O_2 demand by hypertonic saline/dextran was a key factor underlying these resuscitation effects [1].

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