

DTIC FILE COPY

2



AD-A207 250

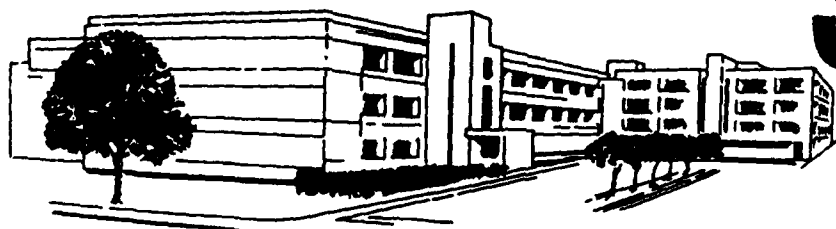
Institute Report No. 369

**Resuscitation of Conscious Pigs Following  
Hemorrhage: Oxygen Delivery and Demand  
During Fixed-Volume Hemorrhage and  
Resuscitation with 7.5% NaCl  
in 6% Dextran**

**J.P. Hannon, C.E. Wade, C.A. Bossone,  
M.M. Hunt, and J.A. Loveday**

***DIVISION OF MILITARY TRAUMA RESEARCH***

**January 1989**



**DTIC  
ELECTE  
APR 28 1989  
S E D**

**LETTERMAN ARMY INSTITUTE OF RESEARCH PRESIDIO OF SAN FRANCISCO CALIFORNIA 94129**

**This document has been approved  
for public release and sale in  
distribution is unlimited.**

**080 4 28 092**

**Resuscitation of Conscious Pigs Following Hemorrhage: Oxygen Delivery and Demand During Fixed-Volume Hemorrhage and Resuscitation with 7.5% NaCl in 6% Dextran *et al.***

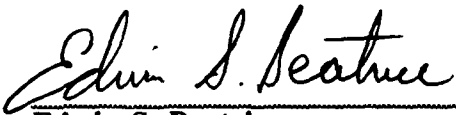
Reproduction of this document in whole or in part is prohibited except with the permission of the Commander, Letterman Army Institute of Research, Presidio of San Francisco, California 94129-6800. However, the Defense Technical Information Center is authorized to reproduce the document for United States Government purposes.

Destroy this report when it is no longer needed. Do not return to the originator.

Citation of trade names in this report does not constitute an official endorsement or approval of the use of such items.

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.

This material has been reviewed by Letterman Army Institute of Research and there is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense. (AR 360-5)

 6 Apr 69  
\_\_\_\_\_  
Edwin S. Beatrice (date)  
COL, MC  
Commanding

This document has been approved for public release and sale; its distribution is unlimited.

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE

## REPORT DOCUMENTATION PAGE

Form Approved  
OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION			1b. RESTRICTIVE MARKINGS		
2a. SECURITY CLASSIFICATION AUTHORITY			3. DISTRIBUTION / AVAILABILITY OF REPORT		
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE			Approved for public release; distribution is unlimited		
4. PERFORMING ORGANIZATION REPORT NUMBER(S) Institute Report No. 369			5. MONITORING ORGANIZATION REPORT NUMBER(S)		
6a. NAME OF PERFORMING ORGANIZATION LAIR, Military Trauma Research		6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION		
6c. ADDRESS (City, State, and ZIP Code) Commander, LAIR/ATTN: SGRD-UL-MTR Presidio of San Francisco, CA 94129-6800			7b. ADDRESS (City, State, and ZIP Code)		
8a. NAME OF FUNDING / SPONSORING ORGANIZATION LAIR		8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER		
8c. ADDRESS (City, State, and ZIP Code)			10. SOURCE OF FUNDING NUMBERS		
PROGRAM ELEMENT NO. 62772A		PROJECT NO. A874	TASK NO. AB	WORK UNIT ACCESSION NO. 092	
11. TITLE (Include Security Classification) Resuscitation of Conscious Pigs Following Hemorrhage: Oxygen Delivery and Demand During Fixed-Volume Hemorrhage and Resuscitation with 7.5% NaCl in 6% Dextran					
12. PERSONAL AUTHOR(S) Hannon, J.P., Wade, C.E., Bossone, C.A., Hunt, M.M. Coppes, R.I., and Loveday, J.A.					
13a. TYPE OF REPORT In-House		13b. TIME COVERED FROM _____ TO _____		14. DATE OF REPORT (Year, Month, Day) Jan 89	
15. PAGE COUNT 16					
16. SUPPLEMENTARY NOTATION					
17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)		
FIELD	GROUP	SUB-GROUP			
19. ABSTRACT (Continue on reverse if necessary and identify by block number)					
<p>A conscious porcine model was used to investigate the adequacy of O<sub>2</sub> delivery relative to O<sub>2</sub> demand, initially during a fixed-volume hemorrhage (37.5 ml/kg over 1 h) and subsequently after resuscitation with 7.5% NaCl/6% Dextran 70 (4 ml/kg). Hemorrhage produced a small increase in O<sub>2</sub> consumption, severe lactacidemia and a doubling of apparent O<sub>2</sub> demand. These effects were attributable to a behavioral compensation (periodic bouts of muscle activity) which presumably served to improve venous return. Despite enhanced ventilator function, O<sub>2</sub> delivery was markedly reduced by hemorrhage, an effect that was due entirely to decrements in cardiac output and hemoglobin level. Resuscitation with 7.5% NaCl/6% Dextran 70 rectified the disparity between O<sub>2</sub> demand, primarily by suppression of demand and secondarily by improvement in delivery.</p> <p><i>conscious porcine model; hemorrhage; resuscitation; hemorrhagic shock; therapy; (47)</i></p>					
20. DISTRIBUTION / AVAILABILITY OF ABSTRACT <input checked="" type="checkbox"/> UNCLASSIFIED/UNLIMITED <input type="checkbox"/> SAME AS RPT. <input type="checkbox"/> DTIC USERS			21. ABSTRACT SECURITY CLASSIFICATION		
22a. NAME OF RESPONSIBLE INDIVIDUAL Edwin S. Beatrice, COL, MC			22b. TELEPHONE (Include Area Code) (415) 561-3600		22c. OFFICE SYMBOL SGRD-ULZ

# ABSTRACT

A conscious porcine model was used to investigate the adequacy of O<sub>2</sub> delivery relative to O<sub>2</sub> demand, initially during a fixed-volume hemorrhage (37.5 ml/kg over 1 h) and subsequently after resuscitation with 7.5% NaCl/6% Dextran 70 (4 ml/kg). Hemorrhage produced a small increase in O<sub>2</sub> consumption, severe lactacidemia and a doubling of apparent O<sub>2</sub> demand. These effects were attributable to a behavioral compensation (periodic bouts of muscle activity) which presumably served to improve venous return. Despite enhanced ventilatory function, O<sub>2</sub> delivery was markedly reduced by hemorrhage, an effect that was due entirely to decrements in cardiac output and hemoglobin level. Resuscitation with 7.5% NaCl/6% Dextran 70 rectified the disparity between O<sub>2</sub> delivery and O<sub>2</sub> demand, primarily by suppression of demand and secondarily by improvement in delivery.

Key Words: Hemorrhage, conscious swine, resuscitation, hypertonic saline/dextran, O<sub>2</sub> delivery, O<sub>2</sub> demand.

Accession For	
NTIS GRA&I	<input checked="" type="checkbox"/>
DTIC TAB	<input type="checkbox"/>
Unannounced	<input type="checkbox"/>
Justification	
By _____	
Distribution/	
Availability Codes	
Dist	Avail and/or Special
A-1	



## INTRODUCTION

The level of blood loss experienced by combat casualties and civilian accident victims is frequently so severe that death ensues in the absence of prompt and effective therapy. In most instances, this therapy is directed at preventing further blood loss and implementing resuscitation procedures that reverse the life-threatening dysfunctions associated with hemorrhagic hypotension. Efforts to improve therapy, and thereby increase the survival incidence of hemorrhage victims, have been commonly based on experimental data, but oftentimes this information is misleading because inappropriate animal models have been used to study the functional effects of hemorrhage. Ideally, an animal model should simulate the physiologic conditions found in human hemorrhage victims, particularly when the research effort is directed at the development of an improved resuscitation procedure. Ethical constraints, e.g. the extensive trauma that so often accompanies severe blood loss in humans, preclude implementing an ideal model. At a minimum, however, the hemorrhage insult should emulate the rate and magnitude of blood loss seen in humans after vascular rupture; it should occur while the animal is in a conscious state to allow full and accurate expression of the normal physiologic changes associated with blood loss; and, if enhanced survival is an endpoint for evaluating efficacy of resuscitation, the hemorrhage insult should be lethal if left untreated. We hope to demonstrate the applicability of such a model in the present communication.

In several species, including pigs [1,2], sheep [3,4], and humans [5,6], small volume resuscitation with hypertonic saline/dextran (7.5% NaCl in 6% Dextran 70) effectively reverses many of the life-threatening dysfunctions associated with hemorrhage. It also provides significant improvement in the survival of animals subjected to lethal levels of blood loss [1,2]. The beneficial effects of hypertonic saline/dextran include a return of cardiac output and arterial pressure to normal or near normal values [1-4], an increase in blood flow to vital organs [7], and a restoration of urine production [3]. These functional improvements are attributable, at least in part, to fluid mobilization from the extra- to the intravascular compartment with consequent increases in blood volume and venous return [1-4]. It is tacitly assumed that the increases in cardiac output and tissue blood flow improve oxygen delivery to previously ischemic tissues, thereby ameliorating the lethal effects of hemorrhage. The validity of this assumption, however, can be questioned, at least insofar as conscious animals are concerned. Few data are thus available on the actual levels of oxygen transport or tissue oxygen demand of conscious animals

subjected to hemorrhage, and no one has investigated these variables following resuscitation with hypertonic saline/dextran.

The foregoing information deficits precipitated the present effort. It was a component of a much larger investigation which compared the resuscitative effectiveness of 0.9% NaCl, 7.5% NaCl, 6% Dextran 70, and 7.5% NaCl/6% Dextran 70 following administration to conscious chronically-instrumented pigs that had been subjected to a lethal fixed-volume hemorrhage [1]. The effort reported here had two specific objectives. The first was to determine the effects of this hemorrhage insult on total body  $O_2$  consumption, apparent  $O_2$  demand and the various functional components of  $O_2$  delivery from ambient air to the body tissues. The second objective was to determine, if possible, whether or not the resuscitative effectiveness of hypertonic saline/dextran was attributable solely to an improvement in  $O_2$  delivery. Our data indicate that the lethality of the hemorrhage model is largely, if not entirely, due to a disparity between  $O_2$  delivery and  $O_2$  demand. Our data also indicate that the resuscitative effectiveness of hypertonic saline/dextran is attributable primarily to a suppression of tissue  $O_2$  demand and secondarily to an improvement of  $O_2$  delivery.

#### METHODS AND MATERIALS

Six immature ( $22.0 \pm 1.75$  kg) Yorkshire pigs were used in this investigation. Seven to 10 days before study they were splenectomized, and were chronically-instrumented with carotid and pulmonary artery catheters and an aortic sideport catheter [8], as described in detail elsewhere [1]. During this same time period, they were trained to accept a respiratory mask and physical restraint in a Pavlov sling.

On the day of study, after an overnight fast, each pig was brought into a quiet laboratory, placed in the Pavlov sling and fitted with the respiratory mask. The mask was connected by means of a 1-way Rudolph valve and 2.5 cm plastic tubing to a Horizons System metabolic apparatus for measurements of respiratory function. The pulmonary and carotid artery catheters were connected to 3-way stopcocks for blood sampling and to pressure tubing and transducers for measurements of hemodynamic function [1]. The animal was allowed to rest quietly in the sling until minimal, but stable, values for  $O_2$  consumption were obtained; the rest interval ranged from 30 to 60 minutes. Three sets of control measurements were then taken at 10 minute intervals. Immediately thereafter, the aortic sideport catheter was opened, and a fixed-volume (37.5 ml/kg) hemorrhage schedule was initiated. Over a subsequent 60 min period, blood was removed progressively on an exponential scale such that

successive 7.5 ml/kg increments had been withdrawn after 9, 19, 31.5, 44, and 60 min. At each of these time points all measurements were repeated. Immediately after hemorrhage, the animal received a 4 ml/kg mixture of 7.5% NaCl/6% Dextran 70, injected into the pulmonary artery over a 1-min time interval. All measurements were again taken at 5, 15, 30, 60, 120, 180, and 240 minutes after the cessation of hemorrhage.

At each measurement point, a 30 ml blood sample was removed from the carotid artery and a 3 ml sample from the pulmonary artery; samples taken during the control and hemorrhage periods were included in hemorrhage volume. These samples were chilled in ice water and then partitioned for a variety of subsequent determinations. The latter included immediate measurement of  $O_2$  content and hemoglobin concentration with an Instrumentation Laboratory Model 282 Cooximeter. Plasma lactate concentration was determined with a GEMSAEC autoanalyzer and Sigmasystem test kits. At all of the foregoing time points, expired ventilation was recorded BTPS, and  $O_2$  consumption and  $CO_2$  production STPD. On the basis of the foregoing measurements, cardiac output values were calculated by the Fick equation and arterial oxygen delivery as the product of arterial  $O_2$  content and cardiac output. Apparent tissue  $O_2$  debt was calculated from the increase in plasma lactate concentration, assuming that 1 mole of  $O_2$  was required to oxidize 2 moles of lactate [9] and that plasma lactate concentration reflected the average concentration in total body water; a value of 640 ml/kg [10] was chosen for the latter. The sum of  $O_2$  consumption and  $O_2$  debt was used to estimate apparent  $O_2$  demand of the tissues. In addition, alveolar ventilation ( $V_A$ ) values were calculated by the Bohr equation:

$$V_A = \frac{(0.867)(VCO_2)}{P_aCO_2}$$

where 0.867 is a constant that converts  $VCO_2$  from STPD to BTPS, assuming a normal porcine body temperature of 38.5C. The shunt fraction of pulmonary blood flow ( $Q_s$ ) was calculated by a modification of the Fick equation:

$$\frac{Q_s}{Q_T} = \frac{C_cO_2 - C_aO_2}{C_cO_2 - C_vO_2}$$

where  $Q_T$  is cardiac output,  $C_cO_2$  is pulmonary end capillary  $O_2$  content,  $C_aO_2$  is arterial  $O_2$  content, and  $C_vO_2$  is mixed venous  $O_2$  content. Temperature and Bohr factors appropriate for the oxyhemoglobin dissociation curve of porcine blood, as reported by Willford and Hill [11], were used in the calculation of  $C_cO_2$  values. Finally, alveolar ventilation and cardiac output values were used to calculate ventilation-perfusion ratios, i.e.  $V_A/Q_T$ .

All data were evaluated with single factor analyses of variance adjusted for repeated measures (time). These analyses were first applied to the hemorrhage period and then to the first hour of the recovery, i.e. before any of the animals had died. Changes were considered significant when  $P \leq 0.05$ . In addition, mean  $\pm$  S.E.M. values were calculated for each time point during 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 S.E.M. values are indicated in the figures that follow.

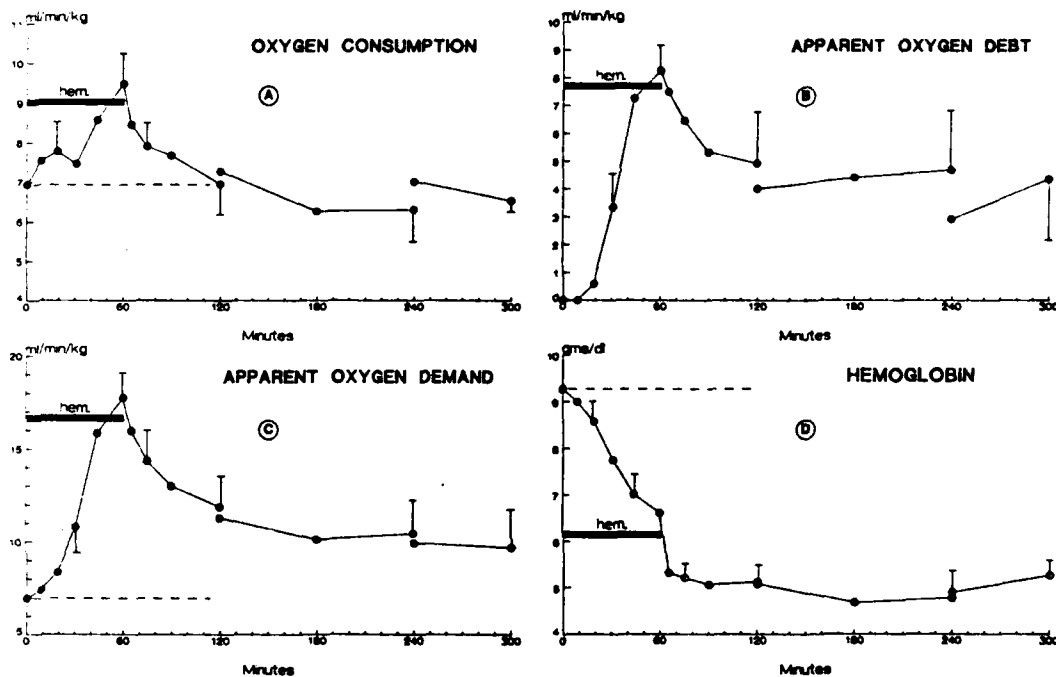
## RESULTS

The responses to hemorrhage in animals described here were not significantly different from those seen in other groups included in the overall investigation [1]. Functional changes produced by the various resuscitation solutions, however, could not be compared because of statistical constraints imposed by nonsurvival of most animals in the other groups [1]. In general, death was preceded by progressively more pronounced hypoventilation, lacticidemia, and hypometabolism. Of the six pigs receiving 7.5% NaCl/6% Dextran 70, 4 survived the complete experimental period and 2 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 [12,13] with equivalently instrumented swine models have shown that none of measured functional variables are appreciably altered as a function of time (up to 6 h).

Hemorrhage was associated with a small, progressive increase in  $O_2$  consumption, the average values rising significantly from a control level of  $6.9 \pm 0.51$  to  $9.5 \pm 0.73$  ml/min/kg at the end of blood removal (Fig.1A). This effect was associated with periodic bouts of muscle activity (leg movements and stretching). During recovery following resuscitation with hypertonic saline/dextran,



O<sub>2</sub> consumption reverted rapidly (within 30 min) to control levels. CO<sub>2</sub> production (not shown) increased to a somewhat greater degree during hemorrhage than O<sub>2</sub> consumption, and as a consequence the respiratory exchange ratio (not shown) was increased significantly, from a control value of  $0.79 \pm 0.036$  to a posthemorrhage value of  $1.06 \pm 0.094$ .



**FIGURE 1.** Effects of progressive fixed-volume hemorrhage (37.5 ml/kg) followed by resuscitation with 7.5% NaCl/6% dextran on total body energy metabolism and hemoglobin level of conscious swine (n=6). 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 the hemorrhage interval, dashed bar the control level for each variable. Significant effects ( $P < 0.05$ ) are indicated in text.

Plasma lactate concentration (not shown), rose significantly during hemorrhage, from  $0.6 \pm 0.04$  to  $13.6 \pm 1.03$  mEq/L. This rise, when calculated in terms of O<sub>2</sub> equivalents represented an absolute O<sub>2</sub> debt of approximately 100 ml/kg. When calculated as a function of time, the apparent O<sub>2</sub> debt thus rose progressively, to  $8.25 \pm 0.87$  ml/min/kg at the end of hemorrhage (Fig. 1B). These changes led in turn to a significant increase in apparent

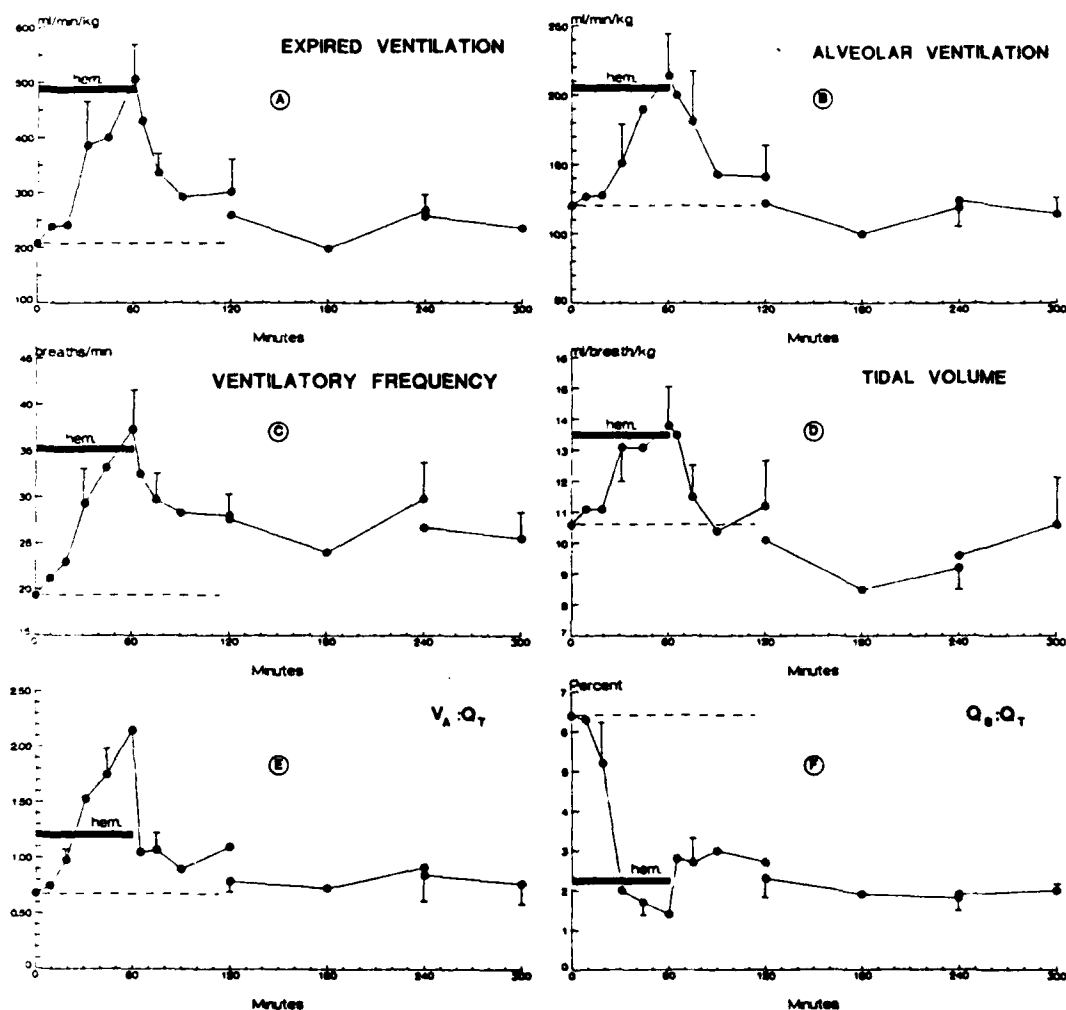
tissue  $O_2$  demand, the sum of  $O_2$  debt and  $O_2$  consumption, from a control level of  $6.94 \pm 0.51$  to  $15.82 \pm 2.36$  ml/min/kg (Fig. 1C). Resuscitation with hypertonic saline/dextran produced a significant reversion of  $O_2$  consumption to control levels and a significant resolution of the increments in apparent  $O_2$  debt and  $O_2$  demand that accrued during hemorrhage.

The hemoglobin concentration of arterial blood decreased significantly during hemorrhage from  $9.3 \pm 0.46$  to  $6.6 \pm 0.37$  g/dl (Fig. 1D). Following administration of 7.5% NaCl/6% dextran, an abrupt further significant decrease to  $5.3 \pm 0.32$  g/dl was observed at 5 min into the recovery period. Thereafter, hemoglobin levels remained relatively stable.

Hypermetabolism during hemorrhage was supported by increased ventilation, the expired values rising significantly from  $208 \pm 23.9$  to  $506 \pm 61.3$  ml/min/kg (Fig. 2A). This response was accompanied by a significant rise in alveolar ventilation from  $120 \pm 12.4$  to  $214 \pm 32.2$  ml/min/kg (Fig. 2B). Hyperventilation was largely, if not entirely, attributable to a significant increase in respiratory rate, from  $19 \pm 1.9$  to  $37 \pm 4.2$  breaths/min (Fig. 2C). Thus, tidal volume (Fig. 2D) rose only slightly during hemorrhage from  $10.6 \pm 0.77$  to  $13.8 \pm 1.16$  ml/min/kg, a change that was not statistically significant. Expired ventilation and alveolar ventilation decreased gradually, but significantly, following resuscitation, and the values approached control levels at 4h into the recovery period.

The combined effects of an increase in alveolar ventilation and a decrease in cardiac output (see below) led to a marked increase in the ventilation:perfusion ratio ( $V_A/Q_T$ ) from  $0.68 \pm 0.048$  to  $2.15 \pm 0.195$  (Fig. 2E). The decrease in cardiac output also caused a significant reduction in pulmonary shunt flow ( $Q_s/Q_T$ ) from  $6.4 \pm 0.42$  to  $1.4 \pm 0.28$  (Fig. 2F). Resuscitation with hypertonic saline/dextran produced an immediate and almost complete reversion of the  $V_A/Q_T$  ratio toward control levels. The  $Q_s/Q_T$  ratio, in contrast, was not altered significantly following resuscitation.

Hemorrhage also led to significant decrements in the  $O_2$  content of arterial (from  $11.7 \pm 0.64$  to  $8.6 \pm 0.49$  ml/dl, Fig. 3A) and mixed venous (from  $7.6 \pm 0.63$  to  $0.97 \pm 0.20$  ml/dl, Fig. 3B) blood. The more pronounced change in the latter resulted in a significant widening of the A-V difference, from  $4.0 \pm 0.16$  to  $7.7 \pm 0.41$  ml/dl (Fig. 3C). Resuscitation with hypertonic saline/dextran had a significant effect on all of these variables: at the 5-min into the recovery period arterial  $O_2$  content was further reduced to  $6.8 \pm 0.40$  ml/dl, mixed venous  $O_2$  content was raised to  $2.5 \pm 0.50$  ml/dl and the A-V  $O_2$  difference

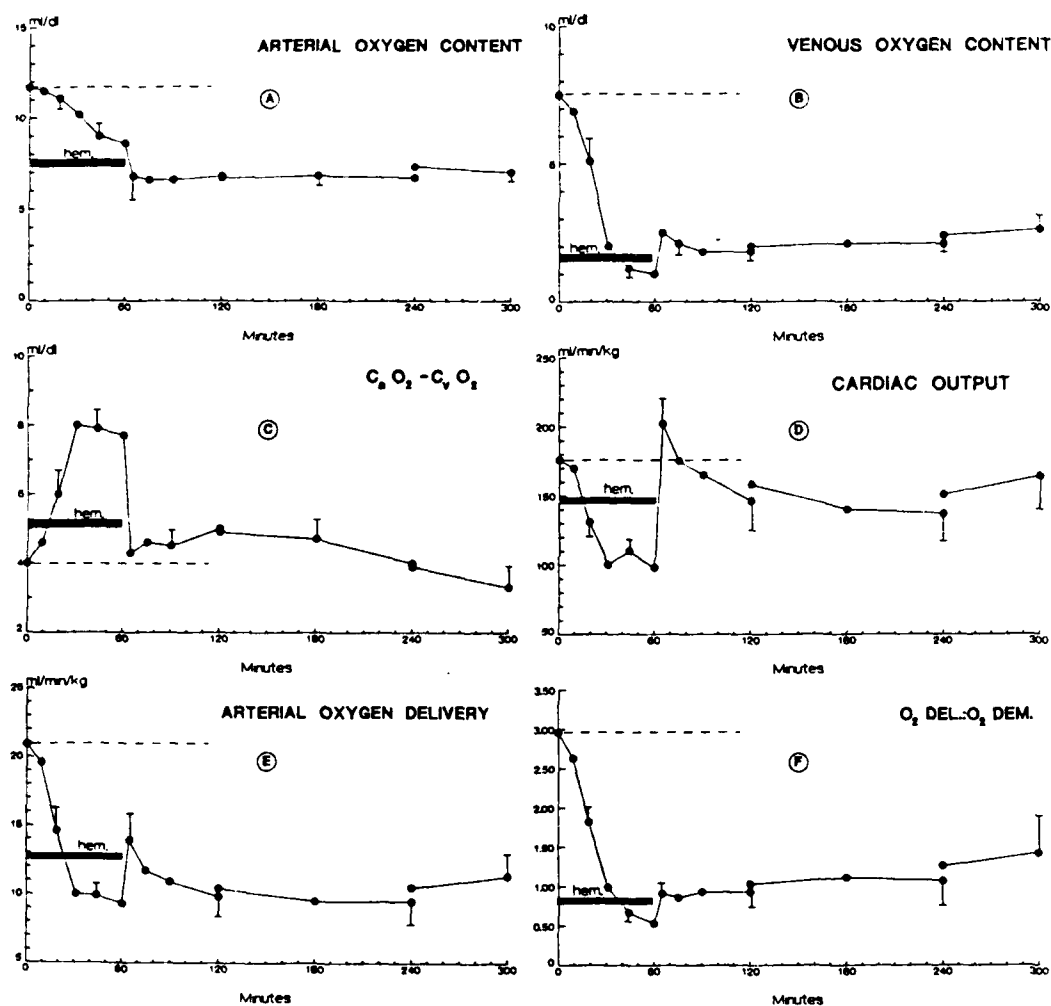


**FIGURE 2.** Effects of progressive fixed-volume hemorrhage (37.5 ml/kg) followed by resuscitation with 7.5% NaCl/6% dextran on pulmonary functions of conscious swine. See FIGURE 1 for other experimental details.

was reduced to  $4.3 \pm 0.39$  ml/dl. The latter value was no different than that observed under control conditions. These acute effects of hypertonic saline/dextran were maintained with little change over the subsequent course of recovery.

A significant decrease in cardiac output during hemorrhage (from  $177 \pm 15.6$  to  $98 \pm 13.9$  ml/min/kg, Fig. 3D) combined with the above-indicated reduction in arterial  $O_2$  content led to a

significant reduction in arterial  $O_2$  delivery (from  $20.9 \pm 2.39$  to  $9.3 \pm 1.14$  ml/min/kg, Fig. 3E). As a consequence of these changes, the ratio of  $O_2$  delivery to apparent  $O_2$  demand was reduced significantly from  $2.96 \pm 0.192$  to  $0.52 \pm 0.055$  (Fig. 3F). In short,  $O_2$  delivery supported about one-half of the  $O_2$  demand.



**FIGURE 3.** Effects of progressive fixed-volume hemorrhage (37.5 ml/kg) followed by resuscitation with 7.5% NaCl./6% dextran on blood oxygen delivery of conscious swine. See FIGURE 1 for other experimental details.

Resuscitation with hypertonic saline/dextran led to a marked and significant increase in cardiac output to  $202 \pm 19.0$

ml/min/kg at the 5-min point in the recovery period. This elevation, however, was not sustained, and after 30 to 60 min the values stabilized at about 80% of the control level. Arterial  $O_2$  delivery showed only transient, and far from complete recovery following administration of 7.5% NaCl/6% dextran. During most of the recovery period the values were essentially the same as those recorded at the end of hemorrhage. The ratio of  $O_2$  delivery to apparent  $O_2$  demand showed a small but significant improvement following hypertonic saline/dextran administration, an effect that was sustained over the remainder of the recovery period.

### DISCUSSION

The foregoing data show that an increasing disparity between  $O_2$  delivery and  $O_2$  demand presents a major threat to the survival of conscious pigs subjected to severe blood loss. This disparity was not attributable to inadequate ventilatory function. Rather, oxygen delivery was compromised by reductions in both arterial  $O_2$  content and cardiac output. The reduction in  $O_2$  content was attributable to transcapillary refill with consequent decrements in hemoglobin concentration and blood  $O_2$  capacity. The accompanying reduction in cardiac output resulted from a progressive decrease in blood volume with consequent decrements in venous return [1]. Apparent oxygen demand, in contrast, rose markedly during hemorrhage. It eventually exceeded  $O_2$  delivery by a factor of at least two, as evidenced by increases in  $O_2$  consumption, plasma lactate concentration and apparent  $O_2$  debt. When unchecked by effective resuscitation, the disparity between  $O_2$  delivery and  $O_2$  demand became progressively more pronounced and eventually led to a decrease in  $O_2$  consumption and a consistently lethal outcome [1].

On the basis of subjective evidence, it appeared that the hemorrhage-induced increase in metabolic rate was due to physical activity (leg movements, stretching, etc.), since cyclical increases in  $O_2$  consumption coincided with periodic bouts of muscle activity. This activity, in our opinion, reflected a behavioral compensation for hemorrhage and served, presumably, to enhance venous return as blood volume was reduced. Such a compensatory response has not been reported previously, insofar as we are aware, perhaps because of constraints inherent in the animal models or procedures that were used in earlier studies of energy metabolism during hemorrhage. Indeed, most [14-22] but not all [23-25] previous reports show that hemorrhage leads to an unchanged [23-25] or reduced [14-22]  $O_2$  consumption. It is perhaps significant that the majority of these investigations involved animals that were anesthetized, subjected to a rapid and sustained reduction in blood pressure (Wiggers procedure), or a combination of these variables. One would not expect to see

muscle activity with a consequent increase in the  $O_2$  consumption of chemically restrained animals, and normal compensatory responses could be overwhelmed or go unobserved in conscious animals subjected to rapid blood loss or the Wiggers procedure. Only Nahas et al [26] have found metabolic increments similar to those reported here. Their results were obtained with anesthetized dogs subjected to a relatively modest, fixed-volume, hemorrhage (25 ml/kg) over a 30 min period with arterial pH maintained within 0.1 unit of 7.40. They [26] attributed the hypermetabolic effect of hemorrhage to sympathetic activation, catecholamine release, and a resultant stimulation of free fatty acid oxidation. This calorogenic effect of catecholamines was observed only in the absence of acidosis [26]. Data recorded in the present study, or obtained coincidentally, are consistent with the observations and interpretations of Nahas et al [26]. Hyperventilation and the blood buffer system effectively compensated for elevated lactic acid production (arterial pH did not change significantly) while plasma concentrations of both epinephrine and norepinephrine rose markedly [27].

It should be emphasized that our calculated values for apparent tissue  $O_2$  demand are only approximations since they are based on lactate accumulation in plasma water and an assumed distribution of lactate in total body water. Knuttgen [9] has shown in human subjects that the  $O_2$  equivalents of lactate, or excess lactate, accumulated during heavy physical work, closely parallel, but underestimate measured  $O_2$  debt. Similar results might be anticipated in the present study since the plasma lactate levels reported by Knuttgen [9] were of the same order of magnitude as those recorded here for pigs. Calculations based on lactate alone underestimate total  $O_2$  debt because a variety of other changes (depletion of body  $O_2$  stores, creatine phosphate, etc.) contribute to an appreciable, alactacid portion of the total debt [28].

The functional mechanisms responsible for the salutary effects of hypertonic saline/dextran 70 are not totally clear, at least in terms of the factors contributing to the adequacy of  $O_2$  delivery relative to tissue  $O_2$  demand. On the delivery side, the improvement in cardiac output shortly after administration of hypertonic saline/dextran was consistent with the reports of others [2-4,7]. The consequent enhancement of arterial  $O_2$  transport, however, was unimpressive, because fluid mobilization during resuscitation produced a sharp decrease in hemoglobin level and blood  $O_2$  capacity.

Suppression of  $O_2$  demand following hypertonic saline/dextran resuscitation appeared to be a far more important determinant of survival. It was a major factor underlying return of A-V

differences in  $O_2$  content to normal levels, a change that indicated adequacy of  $O_2$  delivery relative to demand. The functional changes responsible for the suppression of  $O_2$  demand, however, were not totally resolved in the present study. It was clearly associated with a decrease in muscle activity, but other factors also may have been involved. For example, Nahas et al. [26] showed that acidosis caused a reduction in  $O_2$  consumption during hemorrhage and attributed this effect to an inhibition of catecholamine calorogenesis. Such effects would not be inconsistent with our observations on the actions of hypertonic saline/dextran. Accordingly, other measurements made on these pigs showed a sharp reduction in arterial pH [29] and plasma catecholamine levels [27] shortly after the administration of hypertonic saline/dextran. The interactions of these and other related variables obviously need further investigation.

## REFERENCES

1. Wade CE, Hannon JP, Bossone CA, Loveday JA, Coppes RI, Hunt MM, Gildengoren VL: Resuscitation of conscious pigs following hemorrhage: Comparative effects of 0.9% NaCl, 7.5% NaCl, 6% Dextran 70 and 7.5% NaCl/6% Dextran 70. Presidio of San Francisco, California: Letterman Army Institute of Research, 1988; Institute Report No. 305.
2. Maningas PA, DeGuzman LR, Tillman FJ, Hinson CJ, Priegnitz KJ, Volk KA, Bellamy RF: Small-volume infusion of 7.5 % NaCl in 6% Dextran 70<sup>R</sup> for the treatment of severe hemorrhagic shock in swine. Ann Emerg Med 1986; 15:1131-1137.
3. Kramer GC, Perron PR, Lindsey DC, Ho HS, Gunther RA, Boyle WA, Holcroft JW: Small volume resuscitation with hypertonic saline dextran solution. Surgery 1986; 100:239-247.
4. Smith GF, Kramer GC, Perron P, Nakayama S, Gunther RA, Holcroft JW: A comparison of several hypertonic solutions for resuscitation of bled sheep. J Surg Res 1985; 39:517-528.
5. Holcroft JW, Vassar MJ, Turner JE, Derlet RW, Kramer GC: 3% NaCl and 7.5% NaCl/Dextran 70 in the resuscitation of severely injured patients. Ann Surg 1987; 206:279-288.
6. Maningas PA, Mattox KL, Pepe PE, Jones RL, Feliciano DV, Burch JM: Hypertonic saline-dextran solutions for the prehospital management of traumatic hypotension: A preliminary report. Am J Surg (in press)
7. Maningas PA: Resuscitation with 7.5% NaCl in 6% Dextran 70 during hemorrhagic shock in swine: Effects on organ blood flow. Crit Care Med 1987; 15:1121-1126.
8. Traverso LW: An aortic sideport catheter for rapid hemorrhage of unheparinized swine. Presidio of San Francisco, California: Letterman Army Institute of Research, 1984; Institute Report No. 168.
9. Knuttgen HG: Oxygen debt, lactate, pyruvate, and excess lactate after muscular work. J Appl Physiol 1962; 17:639-634.
10. Bossone CA, Hannon JP: A multi-isotope procedure for simultaneously estimating the volume of body fluid



- compartments of swine. In: Tumbleson ME ed. Swine in Biomedical Research; vol 1. New York: Plenum Press, 1986: 49-60.
11. Willford DC, Hill EP: Temperature corrections for blood gas values. In: Tumbleson ME ed: Swine in Biomedical Research; vol 3. New York: Plenum Press, 1986: 1473-1478.
12. Hannon JP, Bossone CA: The conscious pig as a large animal model for studies of hemorrhagic hypotension. In: Tumbleson ME ed: Swine in Biomedical Research; vol 3. New York: Plenum Press, 1986: 1413-1428.
13. Bossone CA, Loveday JA, O'Benar JD, Hannon JP: Metabolic, cardiovascular, and hormonal effects of morphine in conscious swine. Federation Proc 1987; 46:1478.
14. Baue AE, Tragus ET, Parkins WM: A comparison of isotonic and hypertonic solutions and blood on blood flow and oxygen consumption in the initial treatment of hemorrhagic shock. J Trauma 1967; 7:743-756.
15. Schumacker PT, Long GR, Wood LDH: Tissue oxygen extraction during hypovolemia: role of hemoglobin P<sub>50</sub>. J Appl Physiol 1987; 62:1801-1807.
16. Price PB, Hanlon CR, Longmire WP, Metcalf, W: Experimental shock. I. Effects of hemorrhage in healthy dogs. Bull Johns Hopkins Hosp 1941; 69:327-362.
17. Pardy J, Dudley HAF: Sequential patterns of haemodynamic and metabolic changes in experimental hypovolaemic shock. I. Responses to acute haemorrhage. Br J Surg 1979; 66:84-88.
18. Rothe CF: Oxygen deficit in hemorrhagic shock in dogs. Am J Physiol 1968; 214:436-442.
19. Post RS, Visscher PH, Wiggers C: Sequential changes in oxygen consumption during oligemic and normovolemic shock and their meaning. Am J Physiol 1948; 153:71-80.
20. Chien S, Dellenback RJ, Usami S, Burton DA, Gustavson PF, Magazinovic V: Blood volume, hemodynamic, and metabolic changes in hemorrhagic shock in normal and splenectomized dogs. Am J Physiol 1973; 225:866-879.
21. Smith EE, Crowell JW: Effect of hemorrhagic hypotension on oxygen consumption of dogs. Am J Physiol 1964; 207:647-649.

22. Bruner H, Butzengeiger KH: Über experimentelle Änderungen der Blutmenge. Das Verhalten des Gasstoffwechsels bei Entblutung. Arch Kreislaufforsch 1940; 6:34-46.
23. Kim SI, Desai JM, Shoemaker WC: Sequence of cardiorespiratory alterations after gradual prolonged hemorrhage in conscious dogs. Am J Physiol 1969; 216:1044-1050.
24. Daniel AM, Pierce CH, Maclean LD, Shizgal HM: Lactate metabolism in the dog during shock from hemorrhage, cardiac tamponade or endotoxin. Surg Gynec Obst 1976; 143:581-586.
25. Weiner R, Spitzer JJ: Lactate metabolism following severe hemorrhage in the conscious dog. Am J Physiol 1974; 227:58-62.
26. Nahas GG, Triner T, Small GS, Manger WM, Habif DV: Alterations in O<sub>2</sub> uptake following hemorrhage in dogs. Am J Physiol 1966; 210:1009-1014.
27. Wade CE, Hannon JP, Bossone CA, Loveday JA, Gildengorin VL, Coppes RI, Hunt, MM: Use of a hypertonic/oncotic solution in the treatment of hemorrhage: hemodynamic and hormonal interactions. The Physiologist 1987; 30:229.
28. Astrand PO: Textbook of Work Physiology. New York: McGraw-Hill, 1970.
29. Hannon JP, Bossone CA, Wade CE, Loveday JA: Resuscitation of conscious pigs following hemorrhage: Blood gas and acid-base effects of 7.5% NaCl/6% dextran. FASEB J 1988; 2:A974.

OFFICIAL DISTRIBUTION LIST

Commander

US Army Medical Research  
& Development Command  
ATTN: SGRD-RMS/Mrs. Madigan  
Fort Detrick, MD 21701-5012

Defense Technical Information Center  
ATTN: DTIC/DDAB (2 copies)  
Cameron Station  
Alexandria, VA 22304-6145

Office of Under Secretary of Defense  
Research and Engineering  
ATTN: R&AT (E&LS), Room 3D129  
The Pentagon  
Washington, DC 20301-3080

DASG-AAFJML  
Army/Air Force Joint Medical Library  
Offices of the Surgeons General  
5109 Leesburg Pike, Room 670  
Falls Church, VA 22041-3258

HQ DA (DASG-ZXA)  
WASH DC 20310-2300

Commandant  
Academy of Health Sciences  
US Army  
ATTN: HSHA-CDM  
Fort Sam Houston, TX 78234-6100

Uniformed Services University of  
Health Sciences  
Office of Grants Management  
4301 Jones Bridge Road  
Bethesda, MD 20814-4799

US Army Research Office  
ATTN: Chemical and Biological  
Sciences Division  
PO Box 12211  
Research Triangle Park, NC 27709-2211

Director  
ATTN: SGRD-UWZ-L  
Walter Reed Army Institute of Research  
Washington, DC. 20307-5100

Commander  
US Army Medical Research Institute  
of Infectious Diseases  
ATTN: SGRD-ULZ-A  
Fort Detrick, MD 21701-5011

Commander  
US Army Medical Bioengineering Research  
and Development Laboratory  
ATTN: SGRD-UBG-M  
Fort Detrick, Bldg 568  
Frederick, MD 21701-5010

Commander

US Army Medical Bioengineering  
Research & Development Laboratory  
ATTN: Library  
Fort Detrick, Bldg 568  
Frederick, MD 21701-5010

Commander

US Army Research Institute  
of Environmental Medicine  
ATTN: SGRD-UE-RSA  
Kansas Street  
Natick, MA 01760-5007

Commander

US Army Research Institute of  
Surgical Research  
Fort Sam Houston, TX 78234-6200

Commander

US Army Research Institute of  
Chemical Defense  
ATTN: SGRD-UV-AJ  
Aberdeen Proving Ground, MD 21010-5425

Commander

US Army Aeromedical Research  
Laboratory  
Fort Rucker, AL 36362-5000

AIR FORCE Office of Scientific  
Research (NL)

Building 410, Room A217  
Bolling Air Force Base, DC 20332-6448

USAF School of Aerospace Medicine  
Document Section

USAFSAM/TSKD  
Brooks Air Force Base, TX 78235-5301

Head, Biological Sciences Division

OFFICE OF NAVAL RESEARCH  
800 North Quincy Street  
Arlington, VA 22217-5000