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13. ABSTRACT *(Maximum 200*

In a battlefield environment, it is likely that blood will be in short supply. The logistic problem of providing timely supply of blood to the battlefield and distributing that blood to needed locations will likely keep the supply of blood at levels substantially less than demand. Conservation of this vital resource will be essential. An important part of that conservation is limitation of use of this resource to only when absolutely essential. Accordingly, we attempted to define the human limitation for acute isovolemic anemia (i.e. the "transfusion trigger," the point at which oxygen transport becomes inadequate and transfusion becomes imperative). The research effort was greatly limited as a result of unanticipated truncation in time and funding from the originally approved 3 years to 1 year, with one-third the resources. We studied conscious, unmedicated humans, acutely lowering their blood hemoglobin concentration from normal to 5 g/dL, while maintaining normovolemia. Heart rate, stroke volume and cardiac index increased, systemic vascular resistance and oxygen content and transport decreased. However indicators of adequate tissue oxygen supply, oyxgen consumption and blood lactate concentration did not change. Nor did electrocardiographic monitoring (Holter) indicate the presence of myocardial ischemia. Because we were only able to study 22 rather than the originally proposed and approved 60 people, statistical conclusions from our data are limited: our data indicates that not more than 14% of the normal population would be expected to have inadequate oxygen delivery when hemoglobin concentration is acutely and isovolemically decreased to 5g/dL. This information should aid the medical department in conserving an extremely limited battlefield resource: blood; and decrease the logistic burdens of transportation and storage of blood, as well as to decrease the complications (including transfusion-transmitted viral, parasitic, and bacterial diseases) associated with blood transfusions and decrease the cost (non-return to duty; dollars) associated with those complications. It is recommended that these preliminary data be expanded to allow for these tentative conclusions to reach a greater degree of statistical and scientific probablility.

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FOREWORD

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Richard B. Weiskopf, M.D. 23 Dec 96

PI - Signature Date

TABLE OF CONTENTS

TITLE of Study: Conservation of battlefield blood supply

KEYWORDS: combat injury; hemodilution;

ABSTRACT

In a battlefield environment, it is likely that blood will be in short supply. The logistic problem of providing timely supply of blood to the battlefield and distributing that blood to needed locations will likely keep the supply of blood at levels substantially less than demand. Conservation of this vital resource will be essential. An important part of that conservation is limitation of use of this resource to only when absolutely essential. Accordingly, we attempted to define the human limitation for acute isovolemic anemia (i.e. the "transfusion trigger," the point at which oxygen transport becomes inadequate and transfusion becomes imperative). The research effort was greatly limited as a result of unanticipated truncation in time and funding from the originally approved 3 years to 1 year, with one-third the resources. We studied conscious, unmedicated humans, acutely lowering their blood hemoglobin concentration from normal to 5 g/dL, while maintaining normovolemia. Heart rate, stroke volume and cardiac index increased, systemic vascular resistance and oxygen content and transport decreased. However indicators of adequate tissue oxygen supply, oyxgen consumption and blood lactate concentration did not change. Nor did electrocardiographic monitoring (Holter) indicate the presence of myocardial ischemia. Because we were only able to study 22 rather than the originally proposed and approved 60 people, statistical conclusions from our data are limited: our data indicates that not more than 14% of the normal population would be expected to have inadequate oxygen delivery when hemoglobin concentration is acutely and isovolemically decreased to 5g/dL. This information should aid the medical department in conserving an extremely limited battlefield resource: blood; and decrease the

logistic burdens of transportation and storage of blood, as well as to decrease the complications (including transfusion-transmitted viral, parasitic, and bacterial diseases) associated with blood transfusions and decrease the cost (non-return to duty; dollars) associated with those complications. It is recommended that these preliminary data be expanded to allow for these tentative conclusions to reach a greater degree of statistical and scientific probablility.

1. BACKGROUND

On the battlefield, the logistic burden of transportation and storage of blood will create a shortage of this vital resource. Conservation of blood will be essential. To maximally conserve this limited, vital resource, transfusion on the battlefield must be limited to only those circumstances when absolutely essential. That condition, the "transfusion trigger," the point at which oxygen transport is inadequate and transfusion becomes imperative (i.e. the human limitation for acute isovolemic anemia) is not known. Current red cell transfusion practice is based on beliefs, anecdotal data, or research in laboratory animals. Since the point of critical oxygen delivery varies among laboratory species, information from this source is of limited application for humans. The information gained from this proposed research in humans was to provide clear physiological information indicating when the use of non-oxygen carrying volume replacement (e.g. crystalloid, colloid) should be abandoned and the transfusion of oxygen-carrying fluids begun. This would allow for maximal conservation of what in all likelihood will be an extremely limited, critical, battlefield resource, and allow for "stretching" the limited supply to more of the combat-injured in need of blood.

The product of this research (the ability to transfuse blood at lower hemoglobin concentrations) potentially would offer additional potential benefits: decreasing the logistic burdens of transportation and storage of blood, as well as decreasing the complications (including transfusion-transmitted viral, parasitic, and infectious diseases [hepatitis B virus, hepatitis C virus, hepatitis D (delta) virus, NANB (and non HCV) hepatitis virus, cytomegalovirus, HIV-1 (the virus which causes AIDS), HIV-2 (also capable of causing AIDS), HTLV I/II (the viruses responsible for adult T-cell leukemia and tropical spastic paraparesis), plasmodium (the parasite causing malaria), Trypanosoma cruzi (the parasite causing Chagas'

disease), and a variety of bacteria]) associated with blood transfusions and decrease the cost (non-return to duty; dollars) associated with those complications. Of those developing hepatitis, 50-75% will develop chronic hepatitis, half of these will develop cirrhosis, and half of those with cirrhosis will die of the disease. The current estimate for the risk of developing AIDS following transfusion is approximately 1 in 500,000 transfusions.

Despite technological advances in detecting carriers of these diseases, their potential transmission by blood transfusion will always remain because of limitations of technology (sensitivity and specificity of screening and diagnostic tests) and the possibility of human error in performing those tests. Several strategies have been developed to minimize this risk. Nor is it possible to utilize on the battlefield some alternatives to homologous transfusion, including autologous donation.

Only von Restorff has studied normal conscious, unmedicated chronically instrumented animals (dogs) during acute isovolemic hemodilution.[1] These dogs responded to acute isovolemic decrease in their hematocrit to approximately 12.5% by increasing heart rate and stroke volume, and thus cardiac output, and by lowering peripheral vascular resistance (part, but not all of this decreased SVR may be ascribed to decreased blood viscosity by replacement of red cells with fluid),[2] while arterial blood pressure was unchanged. Although compensation was not perfect and total body oxygen delivery fell, total body oxygen consumption, base-excess, and blood lactate concentration were also unchanged, suggesting that to this level of acute hemodilution, compensation was sufficient to meet metabolic demands. More recently, Levine et al. found that acutely instrumented, restrained baboons did not decrease their oxygen consumption when their hematocrit was lowered from 33% to 15% with a concomitant decrease of oxygen transport from 19 to 11 ml O_2/kg/min. [3]

Further information has only been gathered from anesthetized animals. From a number of investigations, in several species, by several investigators, it appears that *anesthetized* laboratory animals can maintain oxygen delivery and consumption and lack of acidosis until their hematocrit falls to approximately 10-15%[4-9](hemoglobin concentration of approximately 3-5 g/dL). When the hematocrit reaches 10-15% the increase in cardiac output fails to adequately compensate for the decreased hemoglobin concentration: oxygen consumption falls and systemic lactic acidosis develops. In a series of elegant experiments spanning three decades, Cain and his coworkers defined the "critical" level of oxygen delivery required to maintain normal oxygen consumption and prevent the development of systemic acidosis. In anesthetized dogs, the value is approximately 10 ml O_2/kg/min.[4,5] This value may be somewhat less in paralyzed, ventilated baboons,[8] but is much greater for anesthetized rats (approximately 23 ml O_2/kg/min).[6] Experiments examining the impact of isovolemic anemia on specific organ function indicate that myocardial,[7-9] hepatic,[10] and CNS[11] function deteriorate at the same hemoglobin concentration (3-5 g/dL) that causes systemic lactic acidosis.

There are a substantial number of anecdotal reports in the literature suggesting that the lower limit of acute anemia is less than is currently accepted. These reports describe both survivors and deaths of humans at hemoglobin concentrations allowed to become very low because of the patients' refusal to consent to blood transfusion (primarily based on religious belief). These have been reviewed by Viele.[12] The data appear to suggest a lack of mortality at hemoglobin above 5g/dL and a mortality of approximately 50% below that value. Van Woerkens et al. recently reported a "critical" oxygen transport value of approximately 5 ml O_2/kg/min in a paralyzed, ventilated 84-year old "anesthetized" with midazolam.[13] These data were not derived from prospective randomized studies, and thus, it is difficult to draw conclusions.

IN SUMMARY, we had proposed to perform a prospective study and define the "critical" hemoglobin concentration and degree of oxygen transport for conscious humans, thus providing an appropriate data base for those supplying medical care for the combat-injured soldier, which would allow for the safe lowering of the hemoglobin concentration of many soldiers who otherwise would have been transfused with homologous blood. This would potentially conserve the limited battlefield blood resources for those instances when blood is truly needed. Lives would be saved by stretching the available blood supply to those for whom blood would not have been available. The magnitude of the battlefield logistical problem of transportation and storage of blood would be reduced. In addition, the incidence of post-transfusion transmitted diseases would be decreased, thus saving an additional many lives, and dollars associated with the care of the transmitted disorders.

2. HYPOTHESES.

We had hypothesized that:

1. normal, healthy, young humans will respond to acute isovolemic hemodilution by increasing heart rate, stroke volume, and cardiac output, and by decreasing systemic vascular resistance;

2. in young healthy humans, the "critical" level of oxygen transport would be approximately 6-10 ml O2/kg/min at hemoglobin concentrations of approximately 4-5 g/dL.

3. OBJECTIVES

1. Determine the cardiovascular response of conscious, unmedicated normal healthy humans to acute hemodilution.

2. Determine the "critical" hemoglobin level (i.e. the "transfusion trigger" - the hemoglobin concentration at which oxygen transport becomes inadequate and oxygen carrying capacity should be increased).

4. MILITARY SIGNIFICANCE

In a battlefield environment, it is likely that blood will be in short supply. Conservation of this vital resource will be essential. An important part of that conservation would be limitation of use of this resource to only when absolutely essential. Currently, the human limitation for acute isovolemic anemia (i.e. the "transfusion trigger," the point at which cardiovascular compensation fails to meet metabolic need and transfusion becomes imperative) is not known. There are a number of suggestions, but they are based on beliefs, anecdotal data, or research in laboratory animals. Since the response varies among laboratory species, translation of this laboratory data to humans is not possible. The information gained from this proposed research in humans would provide clear, important physiological information indicating when the use of non-oxygen carrying volume replacement (e.g. crystalloid, colloid) should be abandoned and the transfusion of oxygen-carrying fluids begun. This would allow for maximal conservation of what will be an extremely limited battlefield resource. Decreasing the use of blood in any one soldier will increase the amount available for other combat-injured soldiers, and thus save additional lives.

Decreasing the hemoglobin concentration at which blood would be transfused on the battlefield, would also decrease the logistic burdens of transportation and storage of blood, as well as decrease the complications of transfusion-transmitted viral, parasitic, and bacterial diseases associated with blood transfusions and decrease the associated cost (non-return to duty; dollars) of those complications.

IN SUMMARY, our proposed research in humans would allow for the maximal beneficial use of an extremely limited battlefield resource, stored blood.

The research would, thus, also allow for the maximum number of soldiers to be resuscitated with this limited resource, thus also saving lives and maximizing the number returned to duty. In addition, this research would allow for reduction of the logistical burden of transport and storage of blood.

5. EXPERIMENTAL DESIGN AND METHODS

Twenty-two patients with a minimum pre-operative hematocrit of 34%, scheduled for elective orthopedic surgery in which the anticipated blood loss is three to eight units (1500-4000 ml; e.g. extensive corrective spinal surgery, revision of artificial total hip prostheses) or volunteers were studied. Prior to being enrolled each had a routine history and physical examination, and the following laboratory tests: CBC, blood ALT, PT, PTT, fibrinogen, platelet count, and ECG. Criteria for exclusion from the study were (a) clinically significant cardiovascular disease or arrhythmias, (b) taking of medications with cardiovascular actions, including alpha- or beta-adrenergic blocking agents, calcium channel blockers, etc.; (c) moderate or severe pulmonary disease, (d) have a history of abnormal bleeding, known bleeding disorder, or abnormal laboratory coagulation test(s).

The following were placed in each subject with local anesthesia: one or two large-bore peripheral intravenous, a 20 gauge radial artery, and a triple lumen thermodilution flow-directed pulmonary arterial cannulae placed, the latter percutaneously through the internal jugular vein. ECG (usual and Holter) and arterial oxyhemoglobin saturation by pulse oximetry was continuously monitored. Low-flow oxygen via nasal cannulae was provided to maintain arterial oxyhemoglobin saturation ≥98%, (arterial PO_2 110-125, a level which does not add an important amount of dissolved oxygen). After initial cardiovascular measurements were made, whole blood was aseptically removed and simultaneously 5% human serum albumin was infused intravenously to maintain constant central venous and PA "wedge" pressures. Cardiac filling pressures (central venous and "wedge" pressures) were used as the criteria of "isovolemia." Body temperature was measured, using the thermister of the PA cannula, and maintained constant by warming all infused fluids and by external warming of the subject's body, as

necessary. Each 500 ml of autologous whole blood was collected in FDA licensed (to permit reinfusion), sterile blood containers and held at room temperature until reinfusion. Patients' hemoglobin concentrations were progressively lowered by red cell removal and simultaneous fluid infusion until the hemoglobin concentration reached 5 g/dL. Before and after withdrawal of each 500 ml of blood, hemodynamic measurements (systemic and pulmonic arterial systolic, diastolic and mean blood pressures, central venous and pulmonary capillary "wedge" pressures, and cardiac output by thermodilution) were performed, and blood was sampled for measurement of arterial and mixed venous hemoglobin, methemoglobin, and carboxy-hemoglobin concentrations; arterial and mixed venous PO_2, PCO_2, pH, oxygen content, oxyhemoglobin saturation, arterial base-excess, and lactate concentration. From these data the following were calculated: systemic and pulmonary vascular resistances, stroke volume, oxygen transport (TO_2), oxygen consumption (VO_2), and the extraction ratio (VO_2/TO_2). The point of inadequate compensation for acute severe anemia was defined as the point where oxygen consumption decreased, and and blood lactate concentration increased.

B. Methods of data analysis and interpretation:

Data obtained before the administration of any drugs were compared by analysis of variance with repeated measures and Newman-Keuls method of multiple comparisons, and by regression analysis with data subsequent to each isovolemic removal of blood. The "critical" hemoglobin concentration or amount of oxygen transported was defined as that hemoglobin concentration or level of oxygen transport where oxygen consumption was statistically lower, and blood lactate concentration significantly higher than before reduction of hemoglobin concentration.

6. RESULTS

Indices of blood volume: right- and left-heart filling pressures (central venous and pulmonary capillary wedge pressures) did not change with acute severe isovolemic anemia (Figures 1 and 2). Decrease of hemoglobin concentration to 5 g/dL decreased systemic vascular resistance (Figure 3), increased heart rate (from 55 ± 1 b/min to 92 ± 2 b/min, Figure 4, $P<0.05$), stroke volume (from 48 ± 4 ml/m^2 to 63 ± 2 ml/m^2, Figure 5, $P<0.05$), and cardiac index (2.6 ± 0.2 L/m^2 to 5.8 ± 0.2 L/m^2, Figure 6, $P<0.05$. The increase in cardiac index was insufficient to compensate for the decreased arterial oxygen content, resulting in decreased oxygen transport (13.5 ± 1.7 ml O_2/kg/min to 10.1 ± 0.5 ml O_2/kg/min, Figure 7, $P<0.05$), and decreased mixed venous oxyhemoglobin saturation (from 76 ± 4% to 70 ± 1 %, Figure 8, $P<0.05$).

Despite the decreased oxygen transport, oxygen consumption and blood lactate concentration did not change with decreasing hemoglobin concentration (Figures 9 and 10). Oxygen consumption as a function of oxygen delivery was unaltered by the decrease in hemoglobin concentration (Figure 11, linear regression $R^2=0.03$, $P>0.05$). There were no changes, at any time, in the recorded electrocardiogram suggestive of myocardial ischemia. All of the 22 subjects experienced fatigue; however, there were no other symptoms referable to decreased oxygen transport or hypoxia.

Figure Legends

1. Figure 1: central venous pressure (CVP) during progressive acute reduction of hemoglobin concentration to 5g/dL in 22 subjects.

2. Figure 2: pulmonary capillary wedge pressure (Pw) during progressive acute reduction of hemoglobin concentration to 5g/dL in 22 subjects.

3. Figure 3: systemic vascular resistance (SVRI) during progressive acute reduction of hemoglobin concentration to 5g/dL in 22 subjects.

4. Figure 4: heart rate (HR) during progressive acute reduction of hemoglobin concentration to 5g/dL in 22 subjects.

5. Figure 5: stroke volume (SVI) during progressive acute reduction of hemoglobin concentration to 5g/dL in 2 subjects

6. Figure 6: cardiac index (CI) during progressive acute reduction of hemoglobin concentration to 5g/dL in 22 subjects.

7. Figure 7: oxygen transport (TO_2) during progressive acute reduction of hemoglobin concentration to 5g/dL in 22 subjects

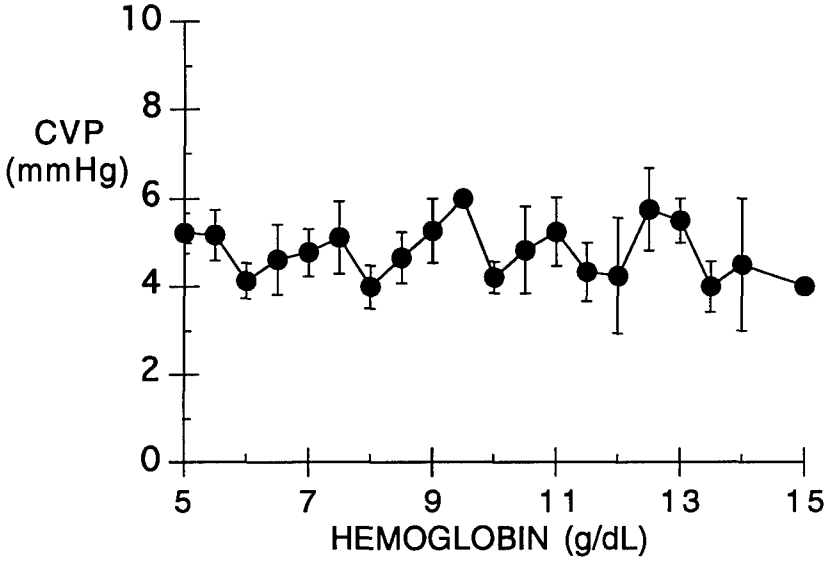
8. Figure 8: mixed venous oxyhemoglobin saturation (SvO_2) during progressive acute reduction of hemoglobin concentration to 5g/dL in 22 subjects.

9. Figure 9: oxygen consumption (VO_2) during progressive acute reduction of hemoglobin concentration to 5g/dL in 22 subjects.

10. Figure 10: blood lactate concentration during progressive acute reduction of hemoglobin concentration to 5g/dL in 22 subjects.

11. Figure 11: oxygen consumption (VO_2) as a function of oxygen delivery (TO_2) during progressive acute reduction of hemoglobin concentration to 5g/dL in 22 subjects.

FIGURE 1:



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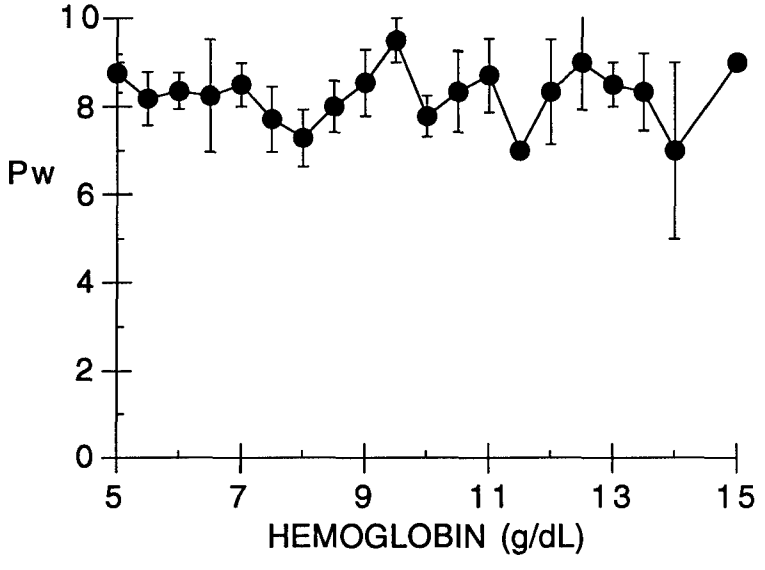

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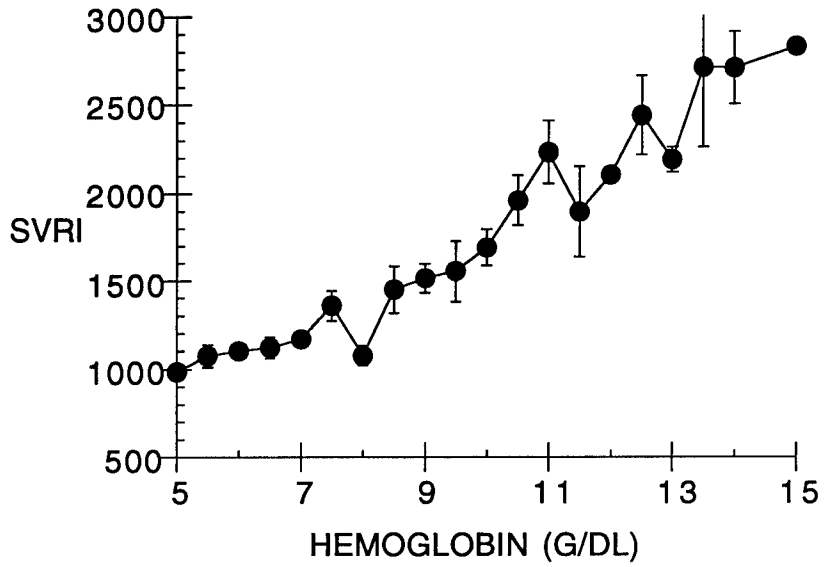

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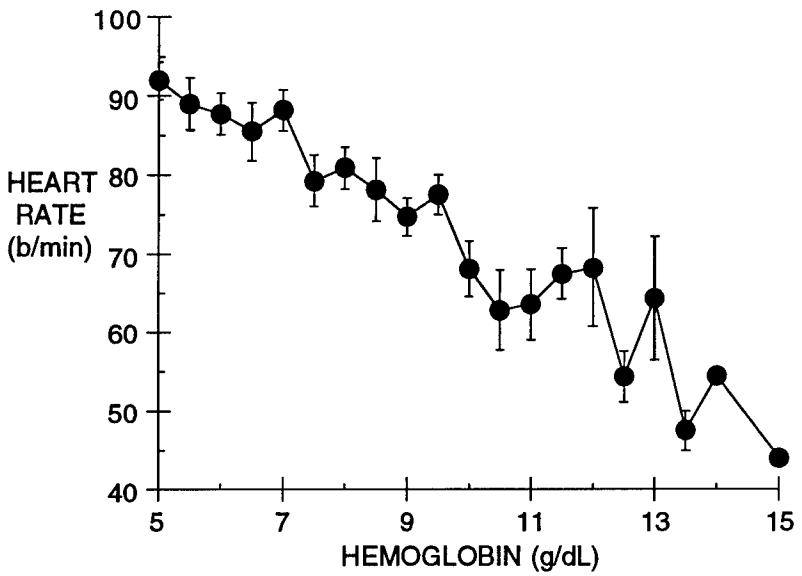

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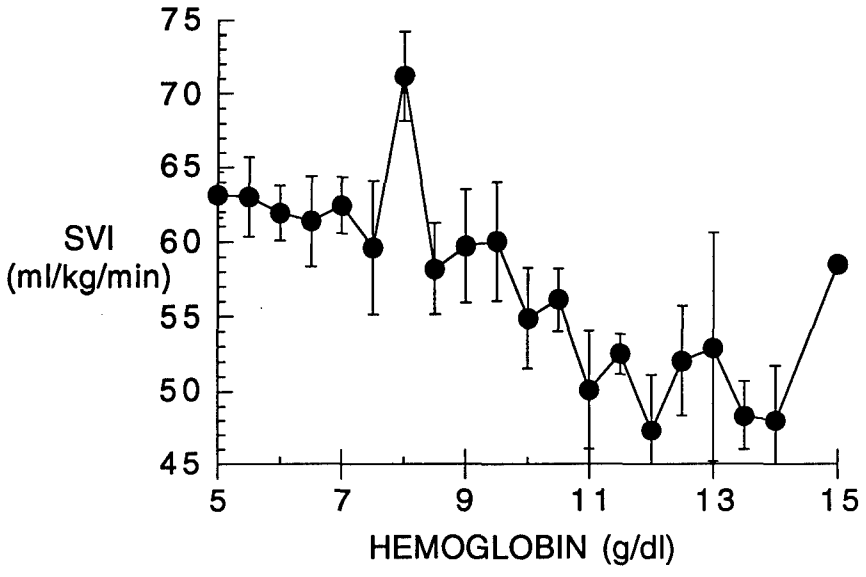

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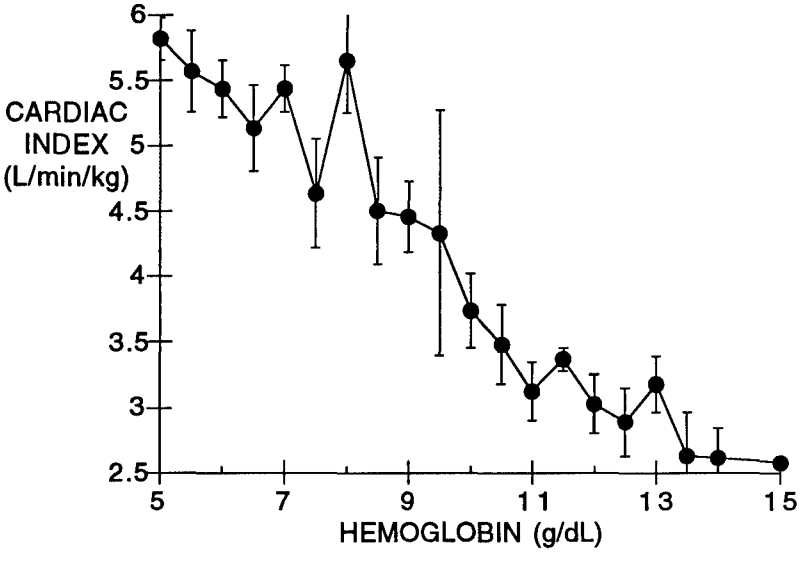

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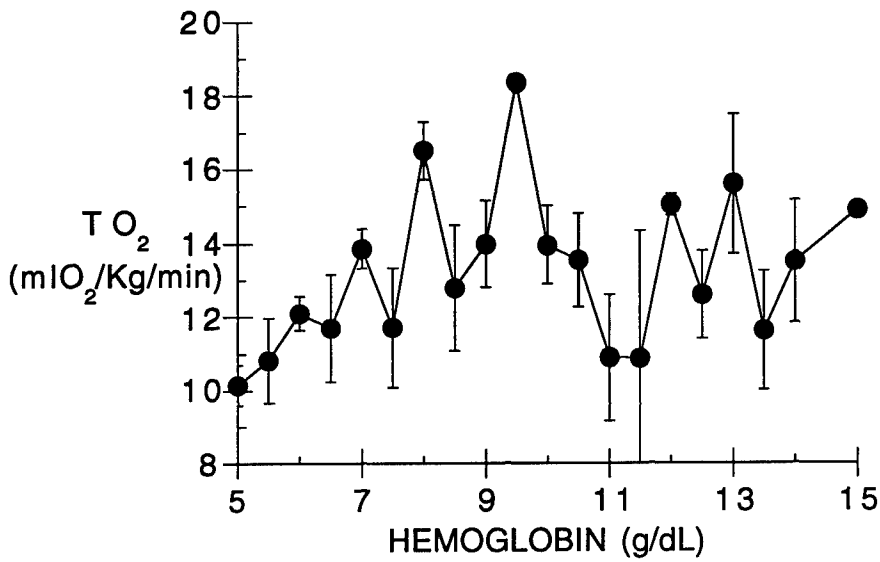

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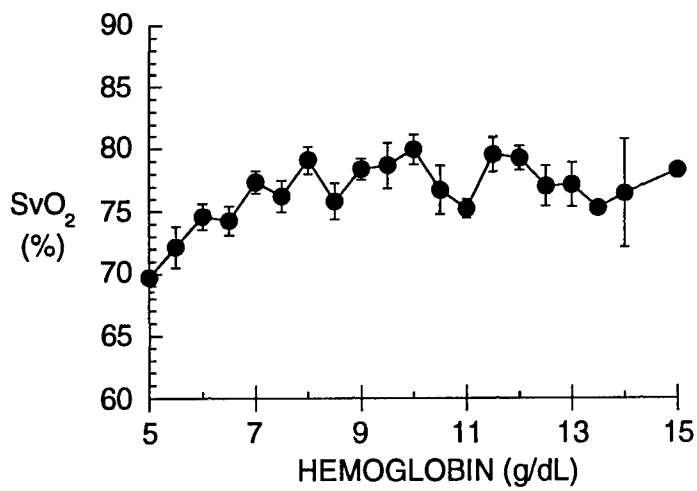

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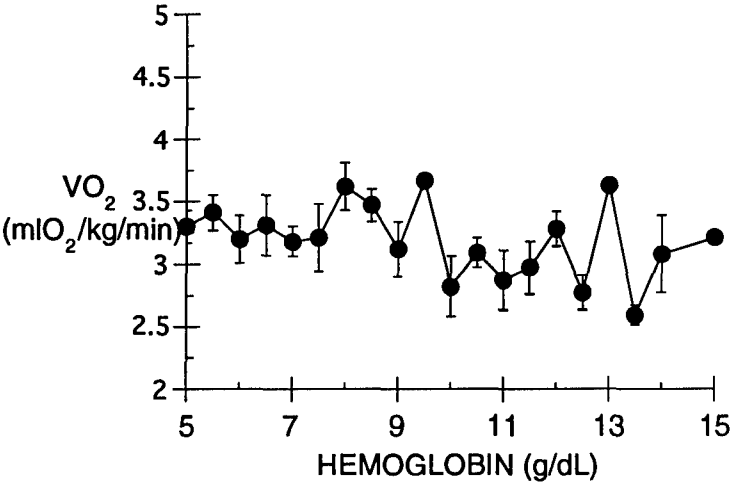

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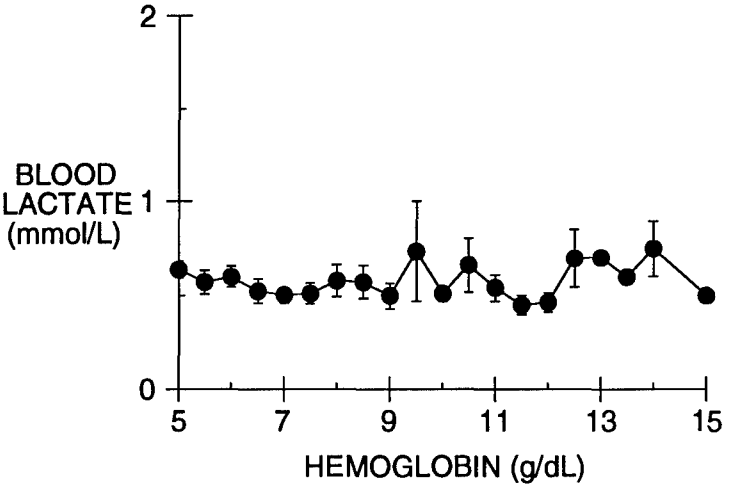

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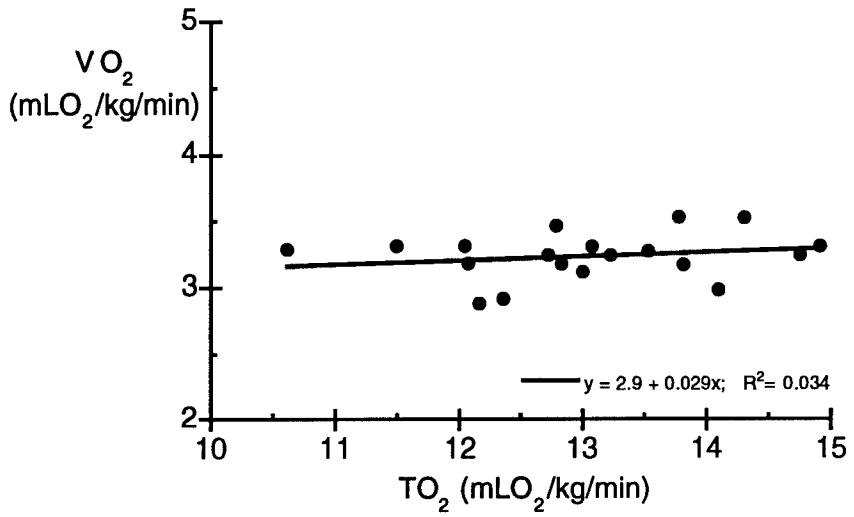
5
4
3
2
VO_2
(mLO_2/kg/min)
y = 2.9 + 0.029x; R^2= 0.034
10
11
12
13
14
15
TO_2 (mLO_2/kg/min)

7. CONCLUSIONS

1. The major finding of this research is that acute reduction of blood hemoglobin concentration to 5 g/dL in conscious healthy people does not apparently result in detectible inadequate systemic or myocardial oxygen delivery. The lack of decreased oxygen consumption, increased blood lactate, or ECG changes in any of the 22 subjects suggests that such changes, with a 95% assurance, would not occur in more than 14% of the population.[14]

2. Unfortunately, owing to the unexpected limitation of funding and time expended for this contract (imposed by the contracting organization) we were unable to achieve the majority of the objectives of the research and cannot state the findings with any further degree of scientific certainty than is indicated above.

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US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
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REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 9 Mar 98

MEMORANDUM FOR Administrator, Defense Technical Information Center, ATTN: DTIC-OCP, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for the following contracts. Request the limited distribution statement for these contracts be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

Contract Number	Accession Document Number
DAMD17-94-J-4407	ADB224557
DAMD17-95-1-5048	ADB230013
DAMD17-95-C-5006	ADB219041
95MM5508	ADB227588
95MM5522	ADB229897
95MM5537	ADB227721
95MM5596	ADB229924
96MM6652	ADB220033
96MM6653	ADB221466
96MM6654	ADB222409

2. Point of contact for this request is Ms. Betty Nelson at DSN 343-7328 or email: betty_nelson@ftdetrck-ccmail.army.mil.

FOR THE COMMANDER:

Phyllis Rinehart

PHYLLIS M. RINEHART
Deputy Chief of Staff for
Information Management

completed
2-8-2000
B.W.