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CARDIOPULMONARY EFFECTS OF ACUTE STRESSFUL EXERCISE
AT ALTITUDE (2300M) OF INDIVIDUALS
WITH SICKLE CELL TRAIT (SCT)

ANNUAL REPORT

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U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

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National Jewish Center for Immunology
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1. PHYSIOLOGIC RESPONSE TO ACUTE STRENUOUS EXERCISE DURING INSPIRATORY HYPOXIA EQUIVALENT TO 4000M IN SCT;

We hypothesized that a greater hypoxic stimulus would significantly potentiate sickling during strenuous exercise, and cause a deterioration in gas exchange and overall O_2 delivery. The present study was designed to evaluate the effect of inspiratory hypoxia equivalent to 4,000m on: -)The performance and physiologic response to acute strenuous exercise of subjects with SCT compared to controls. -)The sickling of red cells and its relationship with exercise performance.

The volunteers were tested under conditions of simulated altitude equivalent to 4,000m ($F_{I}O_2=14\%$; $P_B=656$) and simulated sea level ($F_{I}O_2=24\%$, $P_B=656$ mm Hg). All the subjects undertook one incremental exercise test (Power, VO_2 , VCO_2 , VE, R, V_E/VO_2 , V_E/VCO_2 , HR, O_2 pulse and AT.) and one steady state test (Power, VO_2 , $P_{a}O_2$, $P_{a}CO_2$, pH, HCO_3^- , SaO_2 , O_2 content, V_D/V_T and $P(A-a)O_2$). An antecubital venous catheter was placed in some of the volunteers to measure venous blood gases and % sickling.

Hemogram, SMA 20, Lactic Acid, POsm and UOsm were determined before and after the steady-state exercise tests. At the present time we are in the stage of data collection. We are planning to complete the testing of 30 healthy black males with SCT and 30 controls on August 1987.

2. INTERLABORATORY VARIABILITY OF HEMOGLOBIN S LEVELS (% Hbs) IN SICKLE CELL TRAIT;

To better define the interlaboratory variability of %Hbs, blood samples of 47 healthy black males with SCT (HbAS) were analyzed at an Army Medical Center (Lab. 1) and at a Hb Reference Lab (Lab. 2) utilizing cellulose acetate electrophoresis (pH=8.6). The distribution of %Hbs at Lab. 1 and Lab. 2 was left skewed, non-normal with bimodal tendencies. The %Hbs was higher in the reference lab ($\bar{x} \pm SD = 40.7 \pm 2.7$ VS 35.4 ± 3.0). Variations in technique appear to be responsible for the differences. The observation that 56% of basic trainees with SCT had Hbs > 41% when tested by a Hb Ref Lab reinforces the present Armed Forces Policy of not utilizing an arbitrarily assigned %Hbs in SCT for occupational disqualification. These data confirm the enormity of the interlaboratory variability in %Hbs.

3. SLOWER SINGLE BREATH CARBON MONOXIDE DIFFUSING CAPACITY (DL_{CO}) IN BLACK SUBJECTS COMPARED TO CAUCASIANS;

In view of the well appreciated reduction in lung volumes in Blacks compared to Caucasians, it follows that DL_{CO} in Blacks might also be reduced. Spirometry, lung volumes and DL_{CO} were measured in healthy, young, nonsmoking males with normal CXRs, 55 Caucasians and 55 Blacks. The results confirm the reduction in lung volumes for Blacks compared to Caucasians and at the same time demonstrate a significant reduction of 8% in DL_{CO} for Blacks which when corrected for V_A (DL/V_A) was not significantly different from Caucasians. The reduced DL_{CO} in Blacks is most probably due to the reduction in lung volumes.

4. BASILIC VENOUS BLOOD DURING PROGRESSIVE ONE-ARM EXERCISE.

We studied the effects of progressive one-arm cranking on venous blood from the resting and exercising arms of 16 subjects. In the exercise arm, SvO_2 and CvO_2 decreased significantly during unloaded cranking, but there was no further change with progressive exercise. At peak exercise, both measurements were lower in the exercise arm. A significant increase in CaO_2 and $C(a-v)O_2$ was observed. One-arm exercise did not cause progressive venous desaturation in the exercise arm, probably due to increased oxygen delivery. The results also suggest that there was a redistribution of blood flow from the resting arm to the exercising arm.

5. HAPTOGLOBIN: POOR INDICATOR OF AEROBIC CAPACITY.

To determine whether haptoglobin concentration is an indicator of aerobic capacity, we measured haptoglobin levels and peak oxygen uptake during incremental exercise test in 19 males. The mean haptoglobin \pm SD was 72 ± 41 mg/dl while peak oxygen uptake was $3.34 \pm .52$ L/min. The correlation between these measurements was not significant. We conclude that haptoglobin concentration is a poor index of aerobic capacity.

Recommendations: Haptoglobin is a poor indicator of aerobic capacity in sickle cell trait.

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SUMMARY

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We hypothesized that a greater hypoxic stimulus would significantly potentiate sickling during strenuous exercise, and cause a deterioration in gas exchange and overall O₂ delivery.

The present study was designed to evaluate the effect of inspiratory hypoxia equivalent to 4,000m on: -)The performance and physiologic response to acute strenuous exercise of subjects with SCT compared to controls. -)The sickling of red cells and its relationship with exercise performance.

The volunteers were tested under conditions of simulated altitude equivalent to 4,000m (F_IO₂=14%; P_B=656) and simulated sea level (F_IO₂=24%, P_B=656mm Hg). All the subjects undertook one incremental exercise test (Power, $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E$, R, $\dot{V}E/\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$, HR, O₂ pulse and AT.) and one steady state test (Power $\dot{V}O_2$, PaO₂, PaCO₂, pH, HCO₃⁻, SaO₂, O₂ content, V_D/V_T and P(A-a)O₂.

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FOREWORD

Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

For the protection of human subjects the investigators have adhered to policies of applicable Federal Law 45CFR46.

TABLE OF CONTENTS

	PAGES
SUMMARY.....	2
FOREWORD.....	4
PRELIMINARY COMMENTS.....	6
1. PHYSIOLOGIC RESPONSES TO ACUTE STRENUOUS EXERCISE DURING INSPIRATORY HYPOXIA EQUIVALENT TO 4000m IN SICKLE CELL TRAIT.....	7
-INTRODUCTION.....	8
-MATERIAL AND METHODS.....	11
-COMMENTS.....	15
-REFERENCES.....	16
2. INTERLABORATORY VARIABILITY OF HEMOGLOBIN S LEVELS IN SICKLE CELL TRAIT.....	18
3. LOWER SINGLE BREATH CARBON MONOXIDE DIFFUSING CAPACITY IN BLACK SUBJECTS COMPARED TO CAUCASIANS...	28
4. BASILIC VENOUS BLOOD DURING PROGRESSIVE ONE-ARM EXERCISE.....	40
-INTRODUCTION.....	42
-MATERIAL AND METHODS.....	43
-RESULTS.....	46
-DISCUSSION.....	49
-REFERENCES.....	56
5. HAPTOGLOBIN: POOR INDICATOR OF AEROBIC CAPACITY...	66
-INTRODUCTION.....	68
-MATERIAL AND METHODS.....	69
-RESULTS.....	72
-DISCUSSION.....	73
-REFERENCES.....	78
GLOSSARY.....	84
DISTRIBUTION LIST.....	86

PRELIMINARY COMMENTS

During this time frame we continued to pursue our research mission of establishing the physiologic response characteristics to acute strenuous exercise under adverse environmental conditions in SCT. The question as to whether or not individuals with SCT are at greater risk of developing problems related to exercise and hypoxia remains central to our work. Phase III of our research mission was designed to evaluate the physiologic responses to acute strenuous exercise during inspiratory hypoxia equivalent to 4,000m in sickle cell trait. During this year we have also been involved in the preparation of several manuscripts: "Cardiopulmonary and gas exchange response to acute strenuous exercise at 1,270m in sickle cell trait" and "The effect of army basic training in sickle cell trait." Also some of the data collected in the control group has been analyzed to report interesting physiological findings related to gas exchange, human performance, diffusing capacity, haptoglobin and metabolism and blood flow regulation of the upper body limbs during upper extremity exercise.

PHYSIOLOGIC RESPONSES TO ACUTE STRENUOUS
EXERCISE DURING INSPIRATORY
HYPOXIA EQUIVALENT TO 4000m IN SICKLE TRAIT

INTRODUCTION

Significant controversy persists regarding possible health hazard risks for individuals with Sickle Cell Trait (SCT) when engaged in stressful activities involving exposure to environmental hypoxia and/or strenuous exercise (1). Splenic infarction at altitudes greater than 2100-3000m is a rare but real risk for some individuals with SCT (2). However, the risk can neither be predicted nor quantified. Hypoxia, a potent stimulus for sickling in hemoglobin S (HbS) containing red blood cells, presumably contributes to the pathogenesis of abnormalities experienced at altitude. Strenuous exercise, in turn, has been categorized as a possible independent risk factor in SCT; its relative importance in precipitating splenic syndrome at altitude is uncertain.

It has been speculated that factors present during strenuous exercise, namely acidosis, dehydration, regional hypoxia, and hyperthermia, may promote sickling in vivo (3). The reduced red blood cell flexibility and altered rheology resulting from the generation of sickle shaped erythrocytes would increase the potential for microcirculatory sludging and microvascular occlusion. Moreover, pulmonary microcirculatory involvement would result in arterial hypoxemia and would presumably augment tissue hypoxia and further promote sickle cell formation in the systemic circulation. If significant sickling would occur, tissue ischemia, infarction, and functional impairment would result.

Indeed, a spectrum of exertion induced complications including rhabdomyolysis, disseminated intravascular coagulation, acute renal failure, and even sudden unexpected death (SUD) have been reported in

individuals with SCT (3,4,5). The sequence of events putatively responsible for exertion induced sickling syndromes in vivo remains theoretically very attractive. However, a causal relationship between strenuous exercise and the occurrence of clinically significant sickling syndromes in SCT remains unproven and elusive to demonstrate. Furthermore, past scientific investigations have been inconclusive in providing data upon which cogent statements regarding the risks for these medical complications could be made.

Several groups have studied the role of SCT as an important contributing factor to serious illness occurring during acute strenuous exercise (6,7,8,). Careful review of available physiologic and clinical data of individuals with SCT reveals that the cardiopulmonary and gas exchange responses to acute strenuous exercise as well as the evaluation of exercise performance under environmentally stressful conditions, especially under conditions of environmental hypoxia, has been incompletely investigated. Studies which have evaluated the effect of acute strenuous exercise on sickling have revealed only small amounts of sickled cells immediately post-exercise. No study has evaluated sickling during maximal exercise, and no study has determined whether the presence of hypoxia during exercise would increase the incidence of sickling and whether this would further impair performance.

We have previously demonstrated that the cardiopulmonary and gas exchange responses to brief, strenuous exercise at mild altitude (1270m) and at simulated moderate altitude (2,300m) in SCT were within normal limits and comparable controls (9,10). A subsequent study which evaluated response to physical conditioning was unable to detect

differences in cardiopulmonary parameter between subjects with SCT and controls after seven weeks of Army basic training at 1270m (11).

Having evaluated acute strenuous exercise under conditions of mild and moderate environmental hypoxia, it was only logical to proceed to a greater hypoxic stimulus equivalent to 4000m. Accordingly, the protocol was designed to determine whether the physiologic changes associated with strenuous exercise, especially during exposure to environmental hypoxia equivalent to 4,000m, would promote microcirculatory abnormalities in the lungs and in exercising muscles of individuals with SCT which would result in deterioration in gas exchange and cardiopulmonary performance. Such abnormalities, although clinically inapparent, might produce early subtle evidence for and contribute to clinically significant sickling syndromes. In addition, the extent to which HbS levels and percent sickling determinations correlated with parameters of exercise performance at these varying levels of hypoxia would be addressed.

SUBJECTS AND METHODS

This study was conducted in the Human Performance Laboratory of the William Beaumont Army Medical center, El Paso, Texas, at an altitude of 1270m, mean barometric pressure of 656 mmHg and temperature of 24°C. Sixty healthy, black male basic trainees from Fort Bliss, 30 with sickle cell trait (SCT) (HbAS) and 30 controls (HbAA) participated. Both SCT and control subjects acknowledged voluntary participation in this study by informed written consent. The protocol for this study was approved by the Human Use Committees of William Beaumont Army Medical Center, El Paso, Texas, and the Surgeon General Human Subjects Research Review Board, Falls Church, Virginia. All volunteers were non-smokers and free of intercurrent illness. Thorough evaluation of all subjects showed no abnormalities on medical history, physical examination, posteroanterior and lateral chest x-ray, 12-lead resting electrocardiogram, urinalysis, and standard multi-channel chemistry analyses.

Screening for detection of HbS was performed using the dithionite turbidity test (Ortho). Positive tests were confirmed by cellulose acetate electrophoresis (pH=8.4) with quantitative scanning densitometry (Helena Labs). All individuals with SCT possessed a HbAS electrophoretic pattern. All controls possessed HbAA. All volunteers in both groups had normal values for hemoglobin, hematocrit, red blood cell count, erythrocyte indices, and glucose-6-phosphate dehydrogenase.

Complete pulmonary function testing, including spirometry and lung volumes, were determined in a variable pressure body plethysmograph (Gould 2800 Autobox). Diffusing capacity for carbon

monoxide (DL_{CO}) was performed using a single breath technique (Collins DS520 pulmonary function testing system), and adjusted for altitude by using a diffusing gas mixture with a 24% fraction of inspired oxygen (12). Predicted equations for Caucasians for spirometry, lung volumes, and DL_{CO} (13) were used. Although spirometric standards for healthy black adults have been published (14), they are not widely applied. Suitable predicted equations for DL_{CO} and lung volumes for black adults are not available.

The effect of inspiratory hypoxia on exercise performance was evaluated exercising the volunteers under two environmental conditions: simulated sea level (SSL) which was achieved by changing the fraction of the inspired oxygen to 24% ($P_{I}O_2=146$ mmHg) and simulated 4,000m (S4000m) using a fraction of inspired oxygen of 14% ($P_{I}O_2=85$ mmHg) while maintaining a constant barometric pressure ($P_B=656$ mmHg). For two hours before each exercise test the volunteers breathed either the 14% or the 24 % $F_{I}O_2$ gas mixture (Scott Medical Products, Plumsteadville, Pennsylvania) which was randomly assigned in a single-blind fashion. A respiratory gas mask (Vital Signs) was used with the inspiratory port connected to a 120L reservoir bag supplied from the gas cylinder and the expiratory port open to room air. For the exercise test, the volunteers were changed over to a mouthpiece which was hooked to a two-way respiratory valve (Model 2700 Hans Rudolph) connected to the same gas concentration. Two incremental exercise tests (IET) breathing each one of the gas mixtures were performed on the same day on an electronically braked cycle ergometer (KEM 2). The workload was increased 25-watts every minute until the subject's exhaustion. A two-hour rest period between tests was

allowed.

Minute ventilation (\dot{V}_E), oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and respiratory exchange ratio (R) were measured during exercise in a breath by breath fashion using a computerized system (Medical Graphics Corporation-2000) which integrated flow (pneumotachometer, Hans Rudolph No. 3800) with the respiratory gases measured continuously in the mouthpiece with a mass spectrometer (Perkin-Elmer, MGA-1100) (15).

Anaerobic threshold was determined by an increase in the ventilatory equivalent of oxygen without a corresponding increase in the ventilatory equivalent of carbon dioxide. When a clear breakpoint did not occur, other criteria were used, which included an increase in end-tidal oxygen without an increase in end-tidal carbon dioxide, and/or a significant increase in the respiratory exchange ratio (16). Heart rate (HR) and electrocardiography were monitored continuously during the exercise test with an Anthrometric Electrocardiograph System (Model CC-103). Minute by minute automatic blood pressure determinations were obtained using a Puritan-Bennett Infrasonde D4000.

The next day, two steady state exercise tests (SSET) were performed by each volunteer while breathing either the 14% or 24% $F_{I}O_2$ gas mixture. The order of the gas mixture administered was similar to the IET's order. A two hour rest period was allowed between tests. Each SSET consisted of five minutes of constant power at 50% (SSI) and five minutes at 70% (SSII) of the maximum power achieved during the 14% $F_{I}O_2$ IET. A third level at 70% of the maximum power achieved at 24% $F_{I}O_2$ (SS III) was performed during the

SSET at 24%. A radial arterial catheter was inserted prior to the SSETs for analysis of arterial oxygen tension (P_{aO_2}), arterial carbon dioxide tension (P_{aCO_2}), pH, arterial oxygen saturation (S_{aO_2}) and percent sickling (%S). An antecubital venous catheter was inserted in SCT volunteers for exercise %S and venous blood gases. Some controls had also brachial venous catheters for VBGs. In addition to cardiopulmonary measurements, gas exchange variables which include blood gases, alveolar-arterial gradient [$(P(A-a)O_2)$] and physiologic dead space to tidal volume-ratio (V_D/V_T) were determined at rest and during the last two minutes of each one of the levels of steady state exercise test.

The physiological dead space-tidal volume ratio (V_D/V_T) was calculated using Bohr's formula with the valve dead space being subtracted. The alveolar-arterial oxygen pressure difference [$(P(A-a)O_2)$] was obtained using the mean "ideal" alveolar oxygen tension equation. The arterial blood gases were entered in the computer and the calculations made by the Medical Graphics Corporation System. Percent sickling (%S) was defined as the number of sickled cells expressed as a percent of 500 red blood cells counted on a wet mounted sealed slide of blood fixed in 1% glutaraldehyde phosphate buffer solution. Phase contrast photographs of these wet mount preparation were evaluated by two observers.

The Biomedical Data Package (BMDP) statistical program will be used to compute means, standard deviations and standard error of the means. To detect significant differences for the variables reported in this study, we will use repeated measures analysis of variance (ANOVA) with one grouping variable (2 levels = SCT and controls) and

one within-subject variable, either exercise (2 levels = baseline and peak) or simulated condition (2 levels = SSL and S4000m). When required, two-sample t-tests will be used. A level of 5% ($p < 0.05$) was chosen for statistical significance.

COMMENTS

Presently we are actively involved in the actual testing of subjects for phase III. We anticipate that by August all the experimental part of the protocol should be completed and data collection and statistical analysis will be initiated.

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**INTERLABORATORY VARIABILITY OF HEMOGLOBIN
S LEVELS (%HbS) IN SICKLE CELL TRAIT (SCT)**

BACKGROUND

1. THE ACCURATE DETERMINATION OF HEMOGLOBIN S IDENTIFICATION AND QUANTIFICATION IS CRITICAL NOT ONLY IN THE DIAGNOSES OF THE SICKLE HEMOGLOBINOPATHIES INCLUDING HbAS BUT MAY ALSO BE CRITICAL IN ITS CLINICAL EXPRESSION.
2. FOR INSTANCE, IT HAS BEEN SUGGESTED THAT INDIVIDUALS WITH HbAS HAVING THE HIGHEST HbS LEVELS MIGHT BE MORE SUSCEPTIBLE TO MEDICAL COMPLICATIONS WHICH HAVE BEEN REPORTED IN HbAS SINCE THE AMOUNT OF SICKLE POLYMER IS DEPENDENT UPON THE CELLULAR CONCENTRATION OF HbS. HOWEVER, THE RELATIONSHIP BETWEEN %HbS AND MEDICAL COMPLICATIONS REPRESENTED IN HbAS REMAINS UNCERTAIN. IN ADDITION, THE LACK OF STANDARDIZED METHODOLOGY FOR HbS DETERMINATION IN DIFFERENT HOSPITAL CENTERS FURTHER COMPOUNDS THE PROBLEM.
3. THERE ARE NO STUDIES WHICH HAVE EVALUATED THE CLINICAL IMPACT OF THE VARIABILITY OF HbS VALUES MEASURED IN THE SAME SCT INDIVIDUALS USING DIFFERENT QUANTIFICATION TECHNIQUES.
4. UNTIL 1984, A DEPARTMENT OF DEFENSE REGULATION HAD ESTABLISHED AN ARBITRARY 41% EXCLUSION VALUE FOR SCT WITHIN THE ARMED FORCES. NO ACCOMPANYING DIRECTIVES FOR STANDARDS OF METHODOLOGY WERE ISSUED.

SPECIFIC AIMS

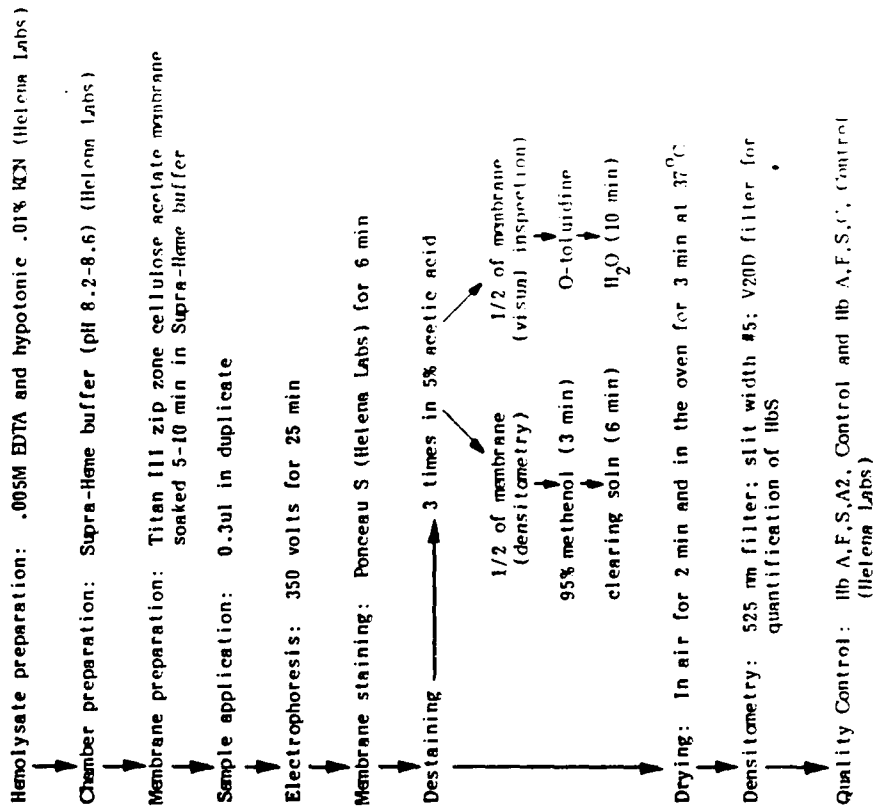
APPRECIATING THAT DIFFERENCES IN %HbS EXIST BETWEEN LABORATORIES, WE SOUGHT:

- 1 - TO QUANTIFY THESE DIFFERENCES.
- 2 - TO CHARACTERIZE THE LEVELS OF %HbS IN HEALTHY BLACK ARMY RECRUITS.
- 3 - TO EXAMINE THE CLINICAL IMPACT OF THE VARIABILITY OF %HbS LEVELS IN HbAS SUBJECTS.

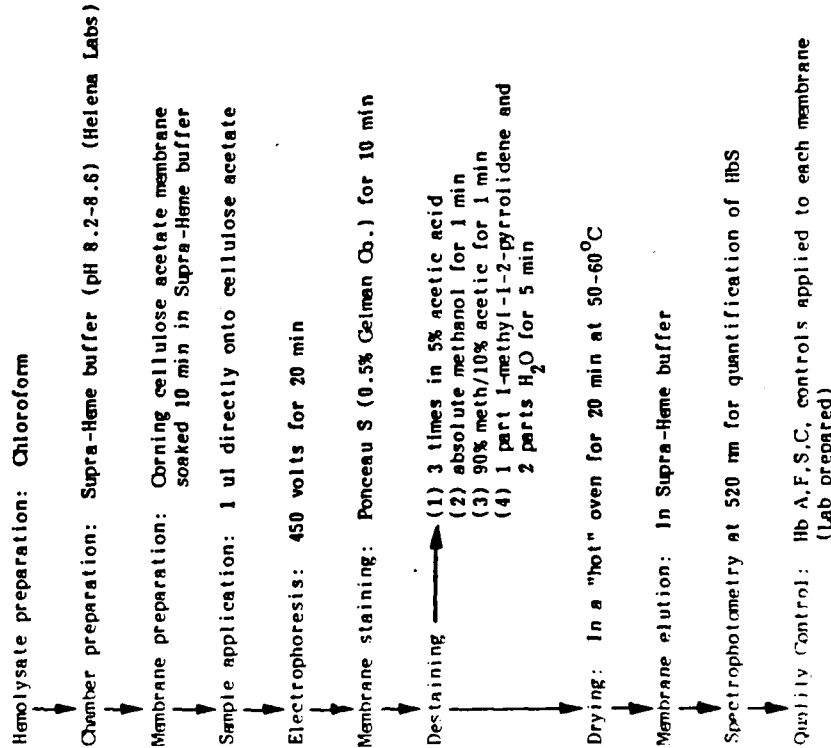
PROTOCOL

ASSESSMENT OF HbS (EXPRESSED AS % OF HbS + HbA) BY CELLULOSE ACETATE ELECTROPHORESIS IN 47 HEALTHY YOUNG BLACK MALES IN TWO LABORATORIES

METHODOLOGY OF LABORATORY 2



METHODOLOGY OF LABORATORY 1



HEMATOLOGIC VARIABLES OF HEALTHY BLACK MALE
VOLUNTEERS WITH SCT (n=47)

	Hb	Hct	RBC	MCV	MCH	MCHC
mean	14.8	44	5.05	88	29	33
<u>+</u> SD	1.4	3.4	0.52	4.5	1.7	1.1

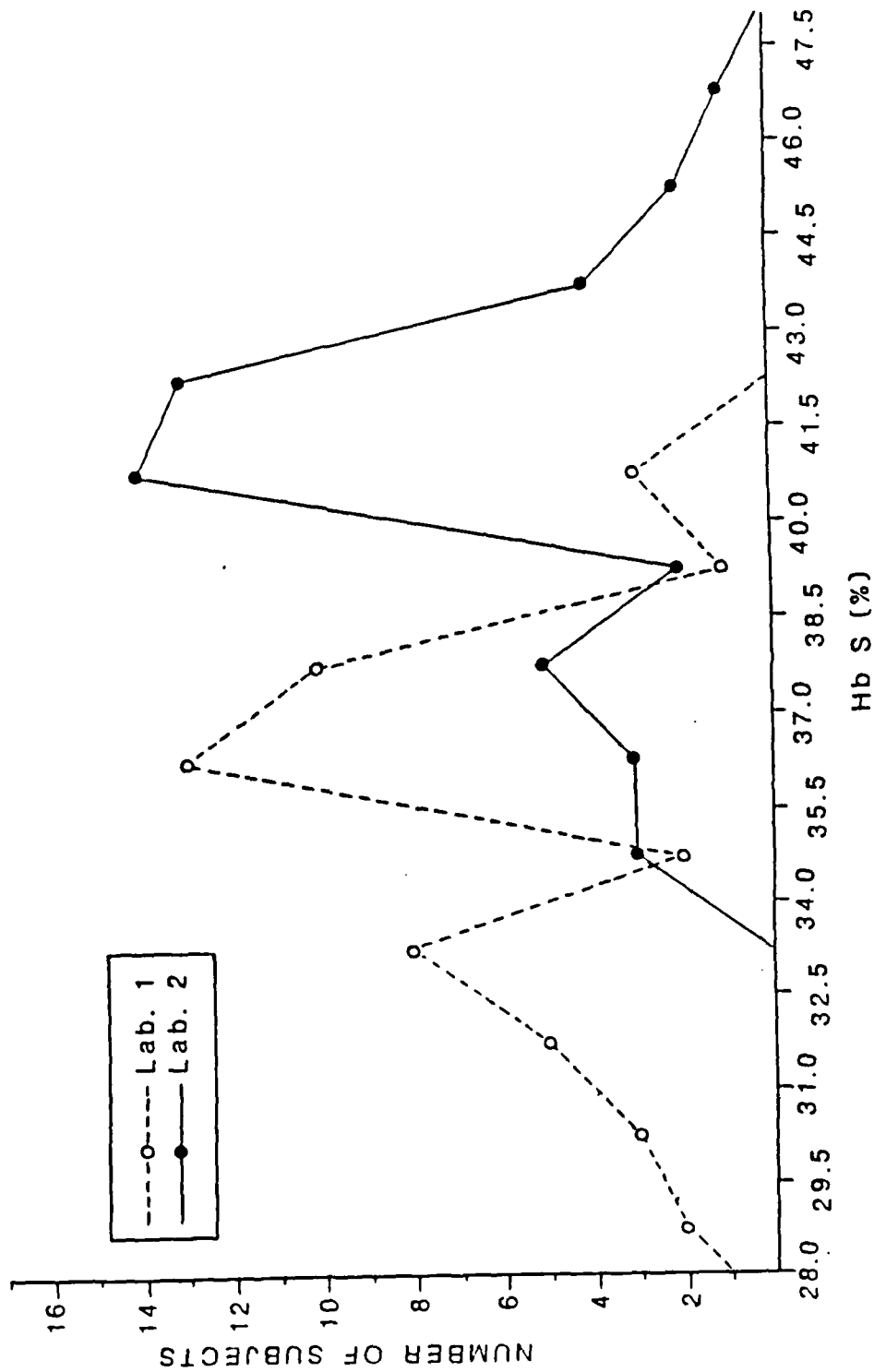
VALUES OF COMMON HEMOGLOBIN VARIANTS
IN THE SCT VOLUNTEERS (n=47)
(Lab. 2)

	HbA(%)*	HbA ₂ (%)*	Hb S(%)*	Hb F(%)**
mean	56.0	3.2	40.7	0.4
<u>+</u> SD	2.6	0.6	2.7	0.4

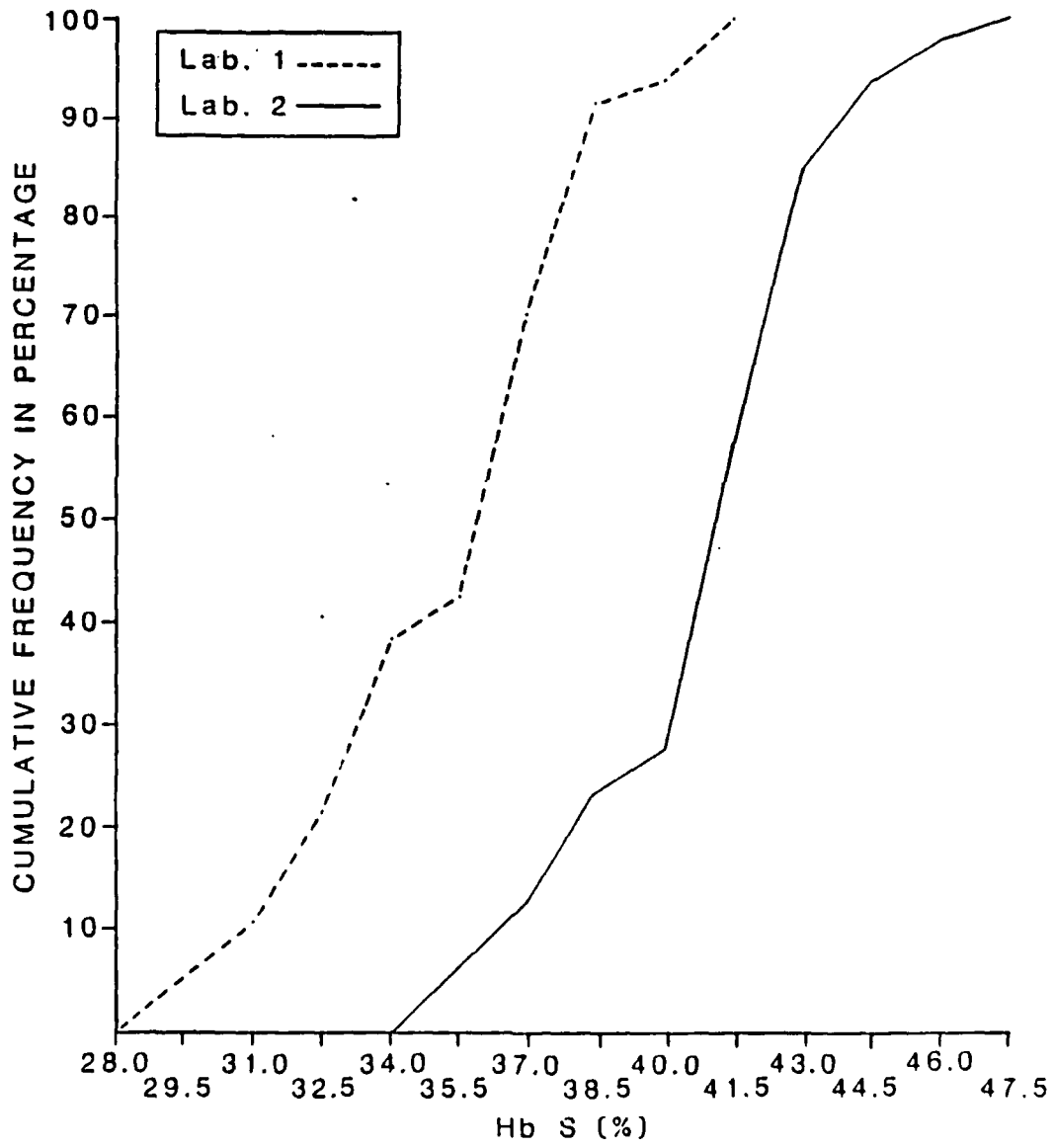
* Expressed as % of HbA + HbS

** Expressed as % of total Hb

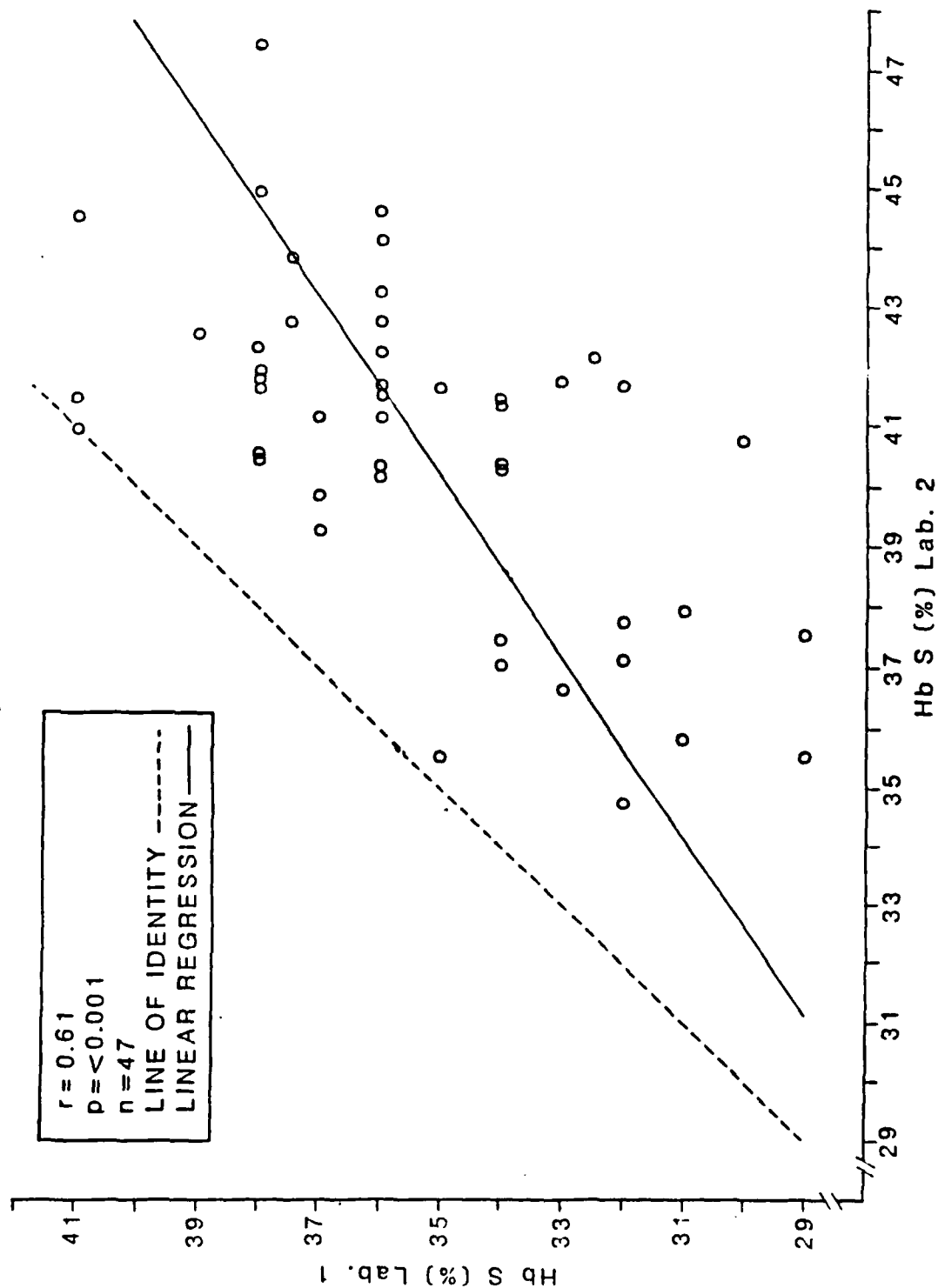
FREQUENCY POLYGONS OF Hb S (%) ASSESSED IN Lab. 1 AND Lab. 2



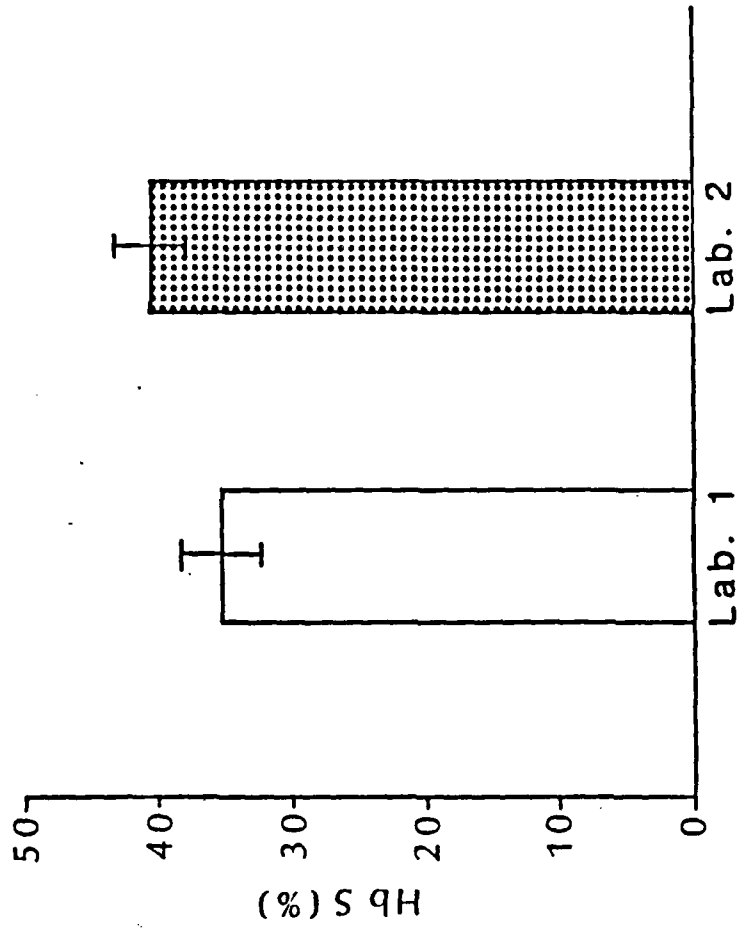
CUMULATIVE FREQUENCIES OF Hb S (%)
ASSESSED IN Lab. 1 AND Lab. 2



RELATIONSHIP BETWEEN Hb S (%) MEASURED IN Lab. 1 AND Lab 2



COMPARISON OF Hb S (%) BETWEEN
Lab. 1 and Lab. 2
($\bar{x} \pm SD$)



SUMMARY AND CONCLUSIONS

1. THE DISTRIBUTION OF HbS(%) HAS A TENDENCY TO BE LEFT SKEWED, NON-NORMAL AND WITH BIMODAL TENDENCIES IN SCT SUBJECTS.
2. HbS QUANTIFICATION UTILIZING DENSITOMETRY (LAB. 2) RESULTED IN CONSISTENTLY HIGHER VALUES (\bar{x} =40.7, RANGE 34.7-47.4%) COMPARED TO SPECTROPHOTOMETRY (LAB. 1) (\bar{x} =35.4%, RANGE 29.0-41.0%). THESE DIFFERENCES MAY REFLECT VARIATIONS IN TECHNIQUE.
3. DATA FROM LAB. 2 ARE CONSISTENT WITH THAT PREVIOUSLY PUBLISHED FOR HbAS. (AM J HEMATOL 1984; 16:123-127)
4. INDEPENDENT OF THE METHOD, NONE OF THE SCT SUBJECTS HAD VALUES OF HbS(%) LOWER THAN 25% OR HIGHER THAN 50%.
5. THIS STUDY SUPPORTS THE PRESENT ARMED FORCES POLICY OF NOT UTILIZING AN ARBITRARILY ASSIGNED VALUE OF % HbS FOR THE PURPOSE OF OCCUPATIONAL DISQUALIFICATION.
6. THESE DATA CONFIRM THE LARGE INTERLABORATORY VARIABILITY IN %HbS DETERMINATIONS AND THE LACK OF A SUITABLE UNIVERSALLY APPLIED QUANTITATIVE HbS "GOLD STANDARD."
7. CAUTION SHOULD THEREFORE BE EXERCISED IN STATEMENTS RELATING INCREASED RISK OF MEDICAL COMPLICATIONS WITH %HbS IN SCT. THE NEED TO CLEARLY SPECIFY THE ELECTROPHORETIC AND QUANTITATIVE METHODS UTILIZED FOR % HbS DETERMINATION IN HbAS IS EMPHASIZED.

**LOWER SINGLE BREATH CARBON MONOXIDE DIFFUSING
CAPACITY (DLCO) IN BLACK SUBJECTS
COMPARED TO CAUCASIANS**

BACKGROUND

- Several anthropometric and physiologic differences are known to exist between black and caucasian subjects.
- Reduced vital capacity has been consistently reported since 1869.
- More recently, reduced total lung capacity has also been demonstrated in black subjects.
- The effect that reduced lung volumes would have on diffusing capacity for carbon monoxide in black subjects compared to caucasians has been incompletely characterized.

$$V = \frac{CS \times A \times T \times (P1-P2)}{\sqrt{MW} \times L \times n}$$

- V = Flow of diffusing gas across respiratory membrane.
CS = Solubility coefficient
A = Respiratory membrane area
T = Gas temperature
(P1-P2) = Transmembrane pressure gradient
 \sqrt{MW} = Molecular weight
L = Length of diffusion

SPECIFIC AIM

To determine whether the diffusing capacity for carbon monoxide in black subjects is reduced compared to a contemporaneous caucasian cohort.

PROTOCOL: SINGLE BREATH CARBON MONOXIDE DIFFUSING CAPACITY

SUBJECTS = 55 blacks and 55 caucasians; healthy, non-smoking males

EQUIPMENT = Automated system Collins DS 520

METHODOLOGY = ESP guidelines except for $F_{I}O_2 = 24\%$

RECALCULATIONS = According to ATS guidelines

- Breath hold time = Ogilvie
- Dead space adjustment = none
- Hb correction = Cotes equation
- COHb correction = none (< 4%)

**PHYSICAL CHARACTERISTICS AND PULMONARY
FUNCTION TESTS†**

	BLACKS Mean ± SEM	CAUCASIANS Mean ± SEM	Δ %
Age (yr)	19±0.2	19±0.2	
Height (cm)	176±0.8	178±0.9	
Hb (g/dl)	14.2±0.1	14.6±0.2	
FVC (L)	4.88±.08*	5.90±.10	17%
FEV ₁ (L/min)	4.14±.06*	4.87±.08	15%
FEV ₁ /FVC (%)	85±0.7*	83±0.7	1%
TLC (L)	6.11±.10*	7.16±.11	15%

†PFT measured in a variable pressure body plethysmograph (Gould 2800 Autobox)

*Significant difference between groups at $p < 0.05$

ALVEOLAR GAS AT PB = 656 mmHg and F_IO₂ = 24%

	BLACKS (n = 25)	CAUCASIANS (n = 23)
	Mean ± SEM	Mean ± SEM
P _A O ₂ (mmHg)	120±0.5*	122±0.8
P _A CO ₂ (mmHg)	30±0.5*	28±0.5

*Significant difference between groups at $p < 0.05$

VENOUS COHb BEFORE AND AFTER DLCO MEASUREMENTS

	BEFORE		AFTER	
	Mean ± SEM	Range	Mean ± SEM	Range
BLACKS (n=38)	0.7±0.07*	0.1-2.0	2.2±0.14*	1.1-3.9†
CAUCASIANS (n=35)	0.9±0.06*	0.4-1.9	2.7±0.10*	1.7-3.7

*Significant difference between groups at $p < 0.05$

†Significant difference after DLCO measurements at $p < 0.05$

**COMPARISON OF DIFFUSING CAPACITY BETWEEN BLACKS
AND CAUCASIANS (ESP GUIDELINES)**

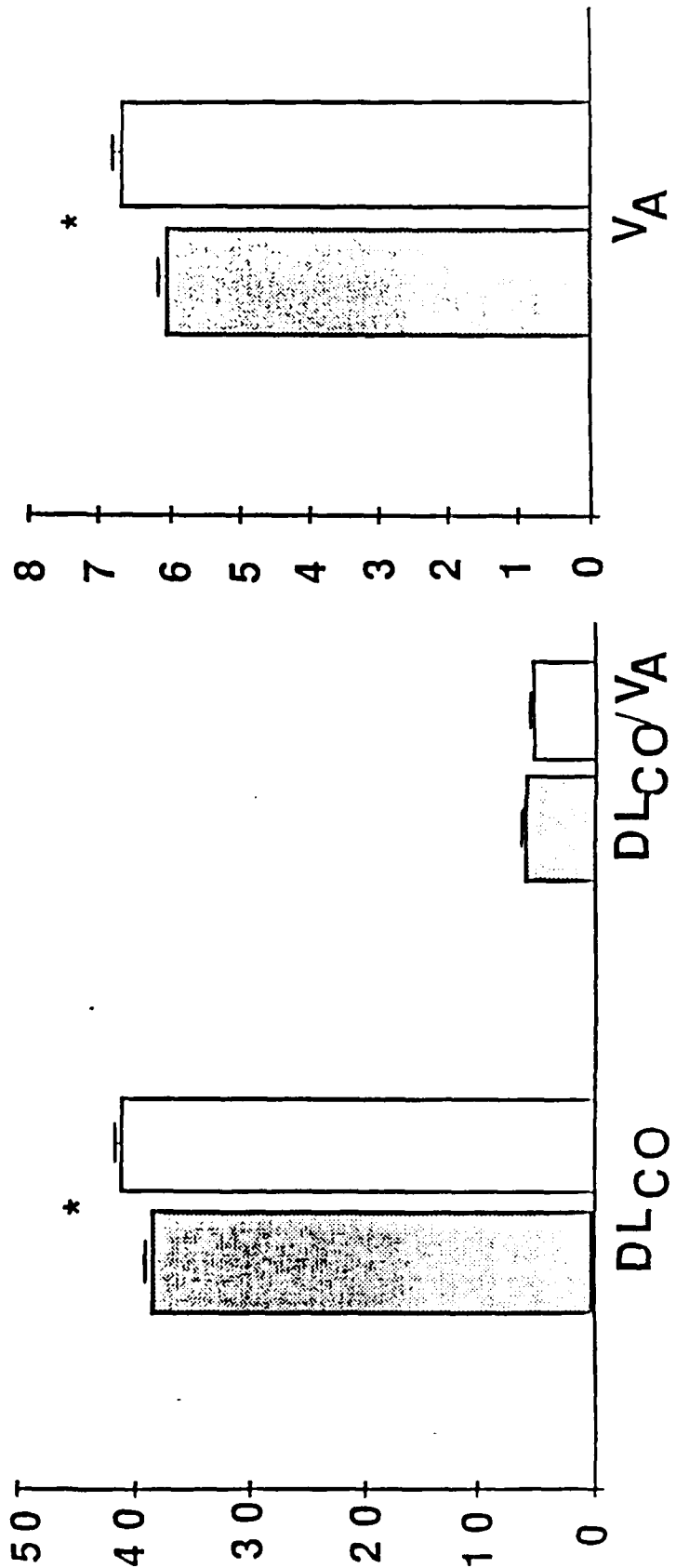
	DLCO (ml/min/mmHg)		V _A (L. BTPS)		DL/V _A (ml/min/mmHg/L)	
	Blacks	Caucasians	Blacks	Caucasians	Blacks	Caucasians
n	55	55	55	55	55	55
Mean	38.2*	41.6	6.07*	6.84	6.4	6.1
SEM	0.7	0.8	0.11	0.12	0.14	0.12
Range	28.2-48.9	24.4-53.1	4.38-8.38	4.68-8.95	4.1-8.8	3.9-8.6
Δ%		8		11		3
% Predicted	93	100	93	101	102	100

†Predicted values from Knudson et al. (*Am Rev Respir Dis* 1987;135:805-811)

*Significant difference between groups at $p < 0.05$

COMPARISON OF DLCO, DLCO/VA, and VA BETWEEN
 BLACKS (■) AND CAUCASIANS (□)
 (ESP GUIDELINES)

* p < 0.05



**COMPARISON OF DIFFUSING CAPACITY BETWEEN BLACKS
AND CAUCASIANS (ATS GUIDELINES)**

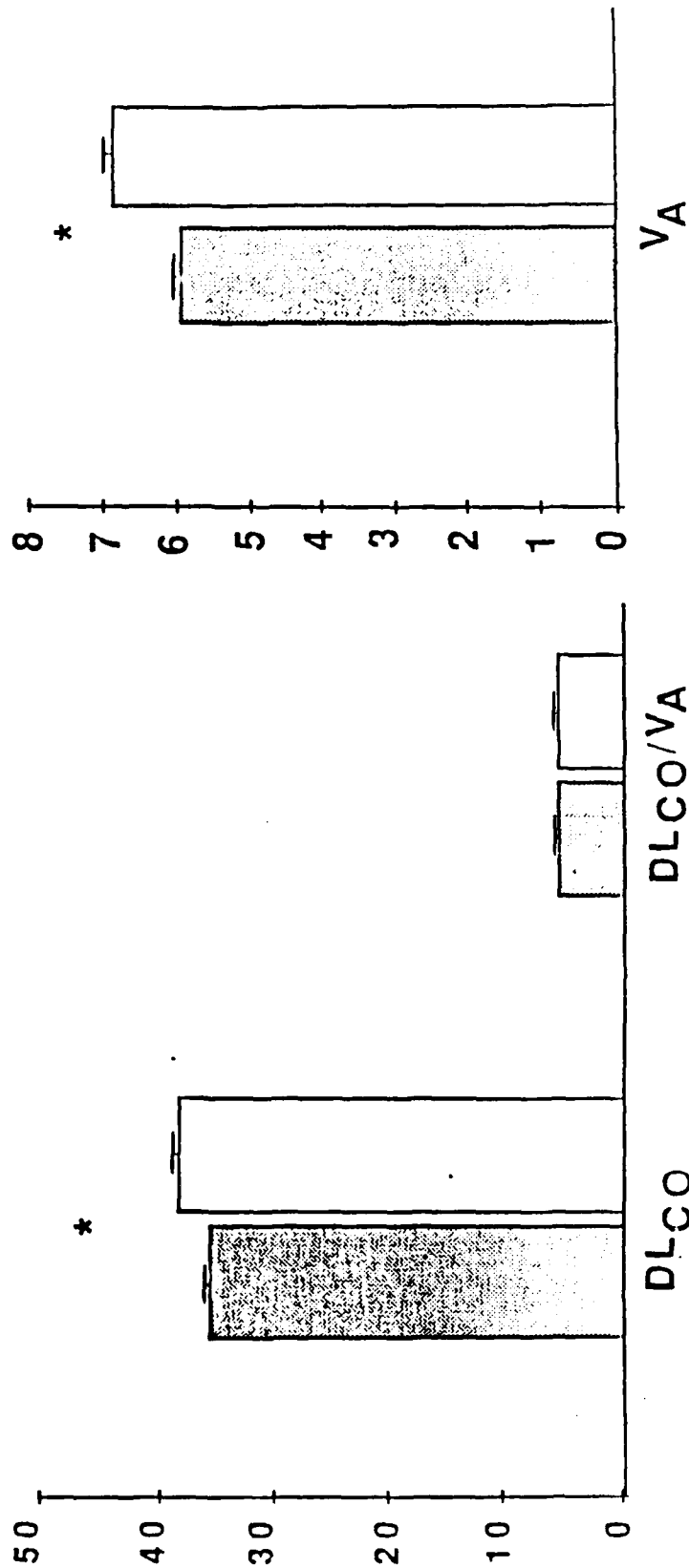
	DLCO (ml/min/mmHg)		V_A (L. BTPS)		DL/ V_A (ml/min/mmHg/L)	
	Blacks	Caucasians	Blacks	Caucasians	Blacks	Caucasians
n	53	50	55	55	53	50
Mean	36.8*	39.7	6.07*	6.84	6.1	5.8
SEM	0.7	0.8	0.11	0.12	0.14	0.12
Range	26.9-46	23.9-52.8	4.38-8.38	4.68-8.95	3.9-8.5	3.9-7.8
Δ %		9		11		4
% Predicted	88	93	91	99	97	94

†Predicted values from Crapo and Morris (*Am Rev Respir Dis* 1981;123:185-189)

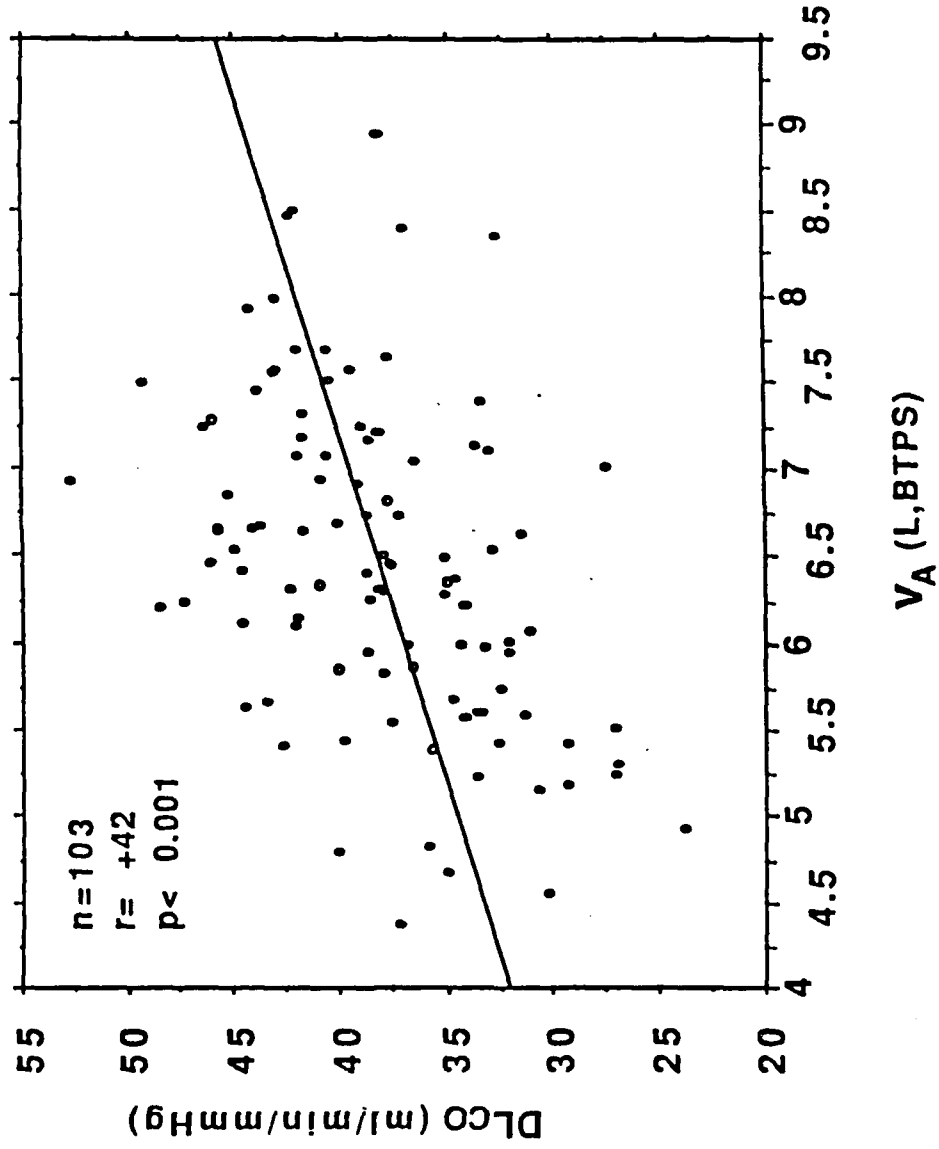
*Significant difference between groups at $p < 0.05$

**COMPARISON OF DLCO, DLCO/VA, and VA BETWEEN
BLACKS (■) AND CAUCASIANS (□)
(ATS GUIDELINES)**

* $p < 0.05$



RELATIONSHIP BETWEEN V_A AND DLCO (ATS GUIDELINES)
FOR POOLED BLACKS AND CAUCASIANS



SUMMARY AND CONCLUSIONS

- D_LCO_{SB} is 8% lower in healthy black male subjects compared to that measured in a contemporaneous caucasian control group.
- When diffusing capacity is expressed per unit of alveolar volume (D_L/V_A), no difference between blacks and caucasians was observed.
- The reduction in lung volumes is most probably responsible for the reduction in D_LCO_{SB} observed in blacks.
- Clinical awareness of the reduction in D_LCO_{SB} in blacks is emphasized; the use of D_L/V_A is recommended.

Basilic Venous Blood
During Progressive One-Arm Exercise

To increase our understanding of the metabolic and circulatory changes which occur during upper body exercise, we studied the effects of progressive one-arm cranking on venous blood from the resting and exercising arms of 16 subjects. In the exercise arm, SvO₂ and CvO₂ decreased significantly ($p < .01$) during unloaded cranking, but there was no further change with progressive exercise. In the rest arm, there was a gradual decrease in SvO₂ and CvO₂ which reached statistical significance during 34 watt cranking. At peak exercise, both measurements were lower ($p < .01$) in the exercise arm (SvO₂: $40 \pm 8\%$ vs. 54 ± 18 ; CvO₂: 8.4 ± 2.1 ml/100ml vs. 11.0 ± 4.2). SvO₂, CvO₂, and PvO₂ increased in both arms after exercise, but the resulting values were higher in the exercise arm. Arterial measurements in 4 exercising subjects revealed a significant increase in CaO₂ and C(a-v)O₂. We conclude that incremental one-arm exercise did not cause progressive venous desaturation in the exercise arm, probably because oxygen delivery increased in proportion to oxygen demand. There was a decrease in SvO₂ and CvO₂ in blood from the rest arm, suggesting that redistribution of blood flow occurred. CvO₂ values after exercise suggest that blood flow to the exercise arm was higher than flow to the rest arm.

Index terms: armcrank, blood flow, venous blood gas, arterial blood gas, metabolism, lactate

Introduction

By increasing metabolism and altering blood flow distribution, exercise affects venous blood in both active and inactive extremities. Several studies have documented significant changes in femoral venous blood during cycle and treadmill exercise (9,10,11,13,15,18,19,21,24). Others have shown that lower extremity exercise alters venous blood in the upper limbs (2,7,13,23,25). Similarly, exercise with one leg has been shown to change venous blood in the nonexercising leg (4,12).

There is less information on the metabolic and circulatory effects of progressive upper extremity exercise on venous blood. Two groups of investigators studied changes in axillary venous blood during two-arm exercise (13,21). The total number of subjects was small and both groups used only two submaximal workloads. Of the two groups, only Freyschuss et al (13) reported venous data collected from the resting legs. In a third study, Ahlborg et al (1) described changes in femoral blood during two-arm exercise, but they did not obtain blood from the exercising arms.

The purpose of this study was to determine the effects of progressive one-arm cranking on venous blood from the resting and exercising arms. This information should increase our

understanding of metabolism and blood flow distribution during upper body exercise.

Methods

Subjects Sixteen healthy males volunteered for the study. The mean age + SD of the subjects was 22 + 1yr, height was 177 + 1cm, and weight was 78 + 3kg. Each subject gave written consent after receiving a detailed explanation of the project. All of the volunteers were physically active members of the U.S. Army. Six subjects had minimal smoking histories (less than two pack-years) and the rest were nonsmokers. Each participant had an unremarkable medical history and a normal physical exam.

Exercise Subjects performed one-arm cranking on a mechanically braked cycle ergometer (Monark 868) that had been modified for armcranking and mounted on a steel stand. The exercising subject sat behind the ergometer with the crankshaft at shoulder height. The arm chosen to exercise was systematically varied between subjects so that both dominant and nondominant arms were used. The arm which wasn't exercising, the "rest arm", was supported by the steel stand during the test. The resting forearm was below the level of the heart, while the upper part of the arm was usually at a 30 degree angle with the body. Subjects were allowed to practice one-arm cranking until they were comfortable with the ergometer.

During the first two minutes of each test, cardiopulmonary measurements were obtained with the subject sitting quietly. The volunteer then began two minutes of unloaded cranking (0W) at a rate of 70 rpm. The power output was then increased 17 watts every two minutes until the subject was unable to maintain a 70 rpm crank rate.

Blood Measurements A 20-gauge catheter was inserted in an antecubital vein of each arm and advanced proximally 20 to 24cm. In all but two subjects, both catheters were inserted in a basilic vein. In those two subjects, one of the catheters was placed in a cephalic vein because of difficulty cannulating the basilic vein in that arm. In both cases, that arm was designated the "rest arm". The last four subjects also had a 15cm 20-gauge catheter inserted into the radial artery of the rest arm. A 20 cm connecting tube with a 3-way stopcock was attached to each catheter to permit blood drawing while the subject exercised. The patency of the catheters and connecting tubes was maintained with a 10 USP units/ml heparin solution.

Blood was drawn simultaneously from each catheter 10 minutes prior to exercise (pre), during the intervals corresponding to 0, 34, and 68 watts, and two minutes after exercise (post). In addition, the three subjects who exercised at 85 watts had blood drawn during this interval and the subjects with arterial

catheters had blood drawn immediately (imm) after exercise. During exercise, blood drawing began approximately 55 seconds into the selected intervals and was completed within 60 seconds.

The PO₂, PCO₂, and pH were determined at 37 degrees C using an automated blood gas analyzer (IL SYSTEM 1304). HCO₃⁻ concentration was calculated by the analyzer using pH and PCO₂. A spectrophotometric oximeter (IL 282 Co-Oximeter) was used to determine hemoglobin concentration and oxygen saturation (SvO₂). Oxygen concentration (CvO₂) was calculated from these measurements by the oximeter. Lactate concentration was determined using an enzymatic method (ACA analyzer).

Cardiopulmonary Measurements Laboratory temperature was maintained at 24 degrees C, while barometric pressure averaged 655 mm Hg. Measurements were done with the subjects breathing through a mouthpiece connected to a pneumotachometer (Hans Rudolph No. 3800) for expiratory volume determination. The fraction of carbon dioxide and oxygen were measured continuously at the mouthpiece using a mass spectrometer (Perkin Elmer, MGA 1100). Data was transmitted to a computer (Medical Graphics Corporation-2000) for integration and breath-by-breath calculation of oxygen uptake (VO₂) and ventilation (VE). Values from the last half of each two-minute interval were reported. Peak oxygen uptake was defined as the highest value per minute achieved during exercise. The ECG was monitored continuously

with an oscilloscope (Anthropometric model cc-103). Heart rate was measured from rhythm strips obtained during the last 5 seconds of each interval and at peak exercise.

Statistical Analysis Values are reported as mean + SD. Venous blood results were analyzed using a two-factor analysis of variance for repeated measures. Arterial measurements were analyzed using a one-factor analysis of variance for repeated measures. When appropriate, individual means were compared using a Fisher PLSD post hoc test. Statistical significance was determined at the 1% level ($p < .01$).

Results

Venous Measurements Venous blood data from both arms was collected from 16 subjects before, during, and after progressive one-arm exercise. The effects of exercise on SvO₂, CvO₂, and PvO₂, are shown in figure 1. After the initial drop during unloaded cranking (the OW interval), there was no significant change in either arm until after exercise. Note that not all values were significantly different from the pre-exercise measurements. Also, oxygen measurements in the exercise arm were usually lower than those in the rest arm. CvO₂ was affected by a

1 g/dl increase in hemoglobin concentration ($p < .01$) which occurred simultaneously in both arms during exercise. Post-exercise, SvO_2 , CvO_2 , and PvO_2 increased significantly in both arms, but the increments were greater and the resulting values were significantly higher in the exercise arm.

Changes in venous pH, PCO_2 , and HCO_3^- are shown in figure 2. The pH in the exercise arm decreased significantly with each increase in workload. In contrast, pH in the rest arm was stable until after the 34W interval. The changes in the arms were not parallel at any time. The $PvCO_2$ in the exercise arm increased significantly with successive increments in power until post-exercise when it decreased significantly. $PvCO_2$ in the rest arm did not change significantly and changes in the arms were never parallel. HCO_3^- in the exercise arm increased significantly during the 0W interval, then remained stable until after the 34W interval when it began decreasing. In the rest arm, HCO_3^- was unchanged until after exercise when it, too, decreased significantly. Changes were parallel between the 0W and 34W intervals.

The average value for each measurement at "peak" exercise is shown in table 1. These values differ slightly from those of the 68W interval because three of the 16 subjects reached the 85W interval.

Arterial Measurements Arterial blood was sampled simultaneously with venous blood in four subjects. Results are graphed in figure 3. Peak exercise mean values, shown in table 1, differ from the 68W values in figure 3 because one of the four subjects reached 85W.

The rise in CaO_2 during exercise was due to an increase in hemoglobin concentration. The arteriovenous oxygen concentration difference ($C(a-v)O_2$) increased in both arms during 0W cranking ($n=4$, $p<.01$), but then remained stable despite progressive exercise. After exercise, $C(a-v)O_2$ declined in both arms but the decrease was greater in the exercise arm.

Lactate Prior to exercise, venous lactate measurements were similar in both arms ($n=16$), while arterial lactate values were slightly lower than the venous measurements in the four subjects in whom it was measured. During 0W cranking, lactate concentration increased in venous blood of the exercise arm and in arterial blood, but it decreased in the rest arm of half the subjects. After the first interval, lactate concentration increased continuously in all samples. Venous measurements in the exercise arm were always higher than those of the rest arm, while arterial measurements were intermediate. Values from a representative subject are shown in figure 4. Mean values at peak exercise are listed in table 1.

Cardiopulmonary Measurements All subjects reached the 68W interval, but only three reached the 85W interval. The relationship between VO₂ and power output is shown in figure 5. Peak exercise measurements for the 16 subjects were: power: 71 + 7W; heart rate: 164 + 19 beats/min; VO₂: 2.12 + .27 L/min; VO₂/kg: 24.4 + 7.8 ml/kg/min; VE: 75.3 + 17.6 L/min.

Discussion

Although there was a decrease in the exercise arm's SvO₂, CvO₂, and PvO₂ during unloaded (0W) cranking, there was no further change as the workload increased. This pattern is similar to that described for two-arm cranking (13,21), but differs from the continuous decrease seen during incremental lower extremity exercise (13,15,18,21). In addition, the oxygen values in basilic venous blood during peak one-arm exercise are much higher than those reported in femoral venous blood during maximal lower extremity exercise (10,15).

There are several possible explanations for these differences. First of all, since skin extracts little oxygen, a higher proportion of blood draining from the skin to the basilic vein could explain the higher oxygen values. Furthermore, an increase in that proportion could have masked desaturation in

blood draining from exercising muscle. However, we don't think this occurred because blood flow to the skin usually remains low during the first 10 minutes of exercise (16) and only a few of our subjects exercised longer than this. Even after 10 minutes, the increase in skin blood flow appears to be minor (16) compared to the amount of blood going to muscle. In addition, if a rise in core temperature caused increased flow to the skin of the exercise arm, then flow to the skin of the rest arm should have increased also. Since CvO_2 and SvO_2 in the rest arm dropped, it's unlikely that blood flow to the skin was increasing. Of course it's possible that local heat production resulted in higher skin flow in the exercise arm (17), but there's still little reason to suspect that blood flow to the skin would increase out of proportion to flow to the exercising muscle.

The location of the catheter may partially explain the stability of venous oxygen measurements in the exercise arm. Since the basilic vein does not drain all the muscles used during one-arm exercise, basilic venous blood may not completely reflect changes in VO_2 . Perhaps basilic CvO_2 was stable because oxygen consumption in the arm reached a maximum during the first stages of exercise, while VO_2 continued to rise because of increased oxygen consumption in the shoulder and trunk muscles. However, since results similar to ours were obtained using a more proximal catheter location (13,21), it's unlikely that catheter placement alone can explain the stability of our venous oxygen measurements.

A more reasonable explanation for the lack of change in the exercise arm's SvO₂ and CvO₂ is that oxygen delivery kept pace with increasing oxygen demand. We suspect that the cardiovascular system is capable of supplying sufficient blood flow to the exercising arm to prevent progressive venous desaturation, unlike the situation during lower extremity exercise. A study which measured xenon clearance during armcrank and cycle exercise indicated that blood flow relative to muscle mass is higher during upper body exercise (6). If flow was indeed high enough to prevent further venous oxygen desaturation, it would appear that because of the relatively small muscle mass involved in one-arm exercise, VO₂ is limited more by the metabolic capacity of the arm than the ability of the cardiovascular system to supply oxygen.

Using Fick's principle, the decrease in CvO₂ in the rest arm (n=16) despite an increase in CaO₂ (n=4) suggests that blood flow to the rest arm decreased. In another study, EMG recordings during one-leg exercise revealed slightly increased activity in the nonexercising leg (1). If similar activity occurred in our subjects' rest arm, then higher VO₂ may have contributed to the decrease in CvO₂. However, since there was no visible movement, we believe that any increase in VO₂ was minimal and that the changes in the rest arm's venous oxygen measurements were due primarily to redistribution of blood flow.

indicate that lactate accumulation during one-arm exercise was not related to basilic PvO₂. Perhaps, as others have suggested, lactate accumulation is due not to anaerobiosis, but to an imbalance between lactate production and clearance (3). The early rise in lactate may have been due to recruitment of type II muscle fibers. The positive arteriovenous lactate difference across the rest arm corroborates previous studies that have demonstrated an increase in lactate uptake by resting muscle (1,4,20).

The average oxygen uptake at peak exercise in this study was higher than that reported by Davies et al (7). Although they, too, studied one-arm cranking, they immobilized each subject's shoulder and trunk, while we did not. The added work necessary to stabilize the torso can probably explain the higher oxygen uptake seen in our subjects.

In conclusion, this study is one of the first to document changes in venous blood during progressive upper body exercise. We found that incremental one-arm exercise does not cause progressive venous desaturation in the exercise arm, probably because oxygen delivery increases in proportion to oxygen demand. We suspect that the relatively small muscle mass used in one-arm exercise can account for the apparent difference between our results and those seen during lower extremity exercise. The decrease in CvO₂ in blood from the rest arm, suggests that redistribution of flow occurs during exercise with small muscle

groups. Finally, venous oxygen measurements increase in both the rest and exercise arm post-exercise, but the higher measurements in the exercise arm suggest that blood flow to the exercise arm is higher.

Acknowledgments

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Table 1. Venous and arterial blood values at peak exercise.

	SO ₂ (%)	CO ₂ (ml/100ml)	PO ₂ (torr)	pH	PCO ₂ (torr)	HCO ₃ ⁻ (meq/L)	Lactate (mmol/L)
Rest Arm (venous, n=16)	54±18	11.0±4.2	32±10	7.34±.04	46±5	26±3	3.7±1.4
Exercise Arm (venous, n=16)	40±8	8.4±2.1	29±3	7.20±.04	66±8	25±2	9.6±2.5
Arterial (n=4)	96±1	20.2±2.2	96±5	7.37±.02	33±2	19±1	7.8±.8

Values are means ± SD

Figure Legends

Figure 1- Venous oxygen saturation (SvO_2), concentration (CvO_2), and PvO_2 in the rest and exercise arm, during and after progressive one-arm exercise ($n=16$). Values are mean \pm S.D. "*" indicates significantly different from pre-exercise value ($p<.01$). "+" indicates significant difference between arms during that interval ($p<.01$).

Figure 2- Venous pH, PCO_2 , and HCO_3^- concentration in the rest and exercise arm, during and after progressive one-arm exercise ($n=16$). Values are mean \pm S.D. "*" and "+" are same as for figure 1.

Figure 3- Arterial measurements during and after progressive one-arm exercise ($n=4$). Values are mean \pm S.D. "*" is same as for figure 1.

Figure 4- Lactate concentration in arterial blood, venous blood from the rest arm, and venous blood from the exercise arm, during and after progressive one-arm exercise. Values are from one subject.

Figure 5- Relationship between power output and oxygen uptake during progressive one-arm exercise. Values are mean \pm S.D. Only three of the 16 subjects reached the 85W interval.

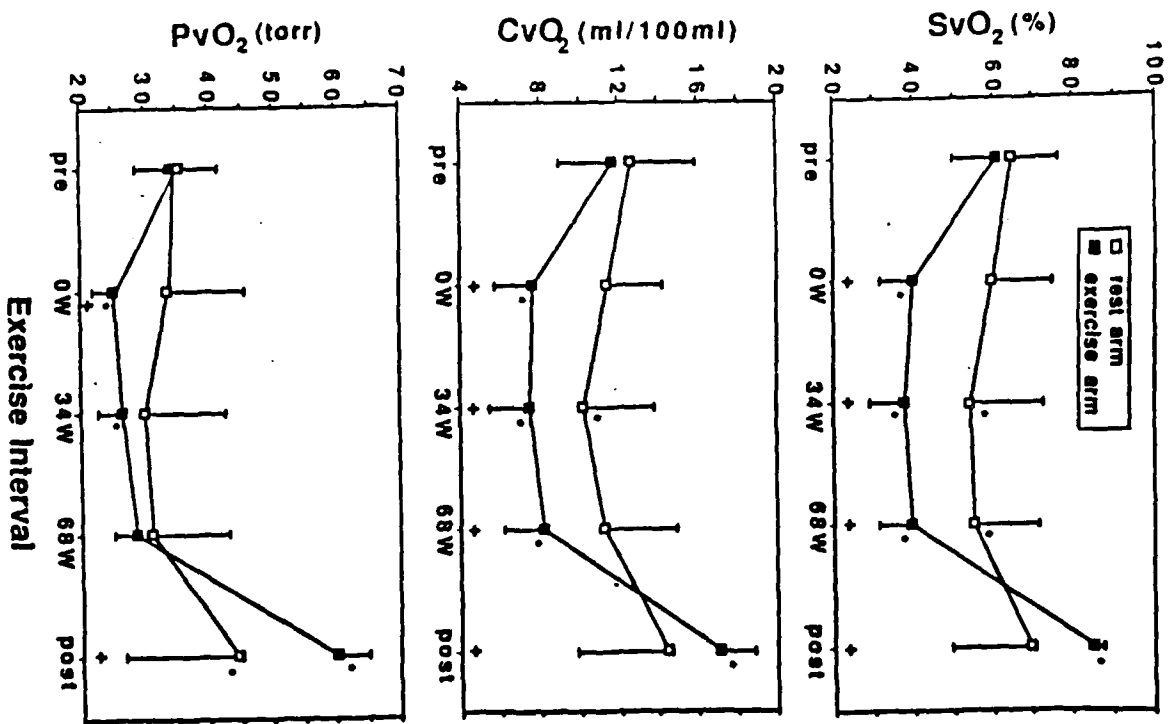


Fig. 1

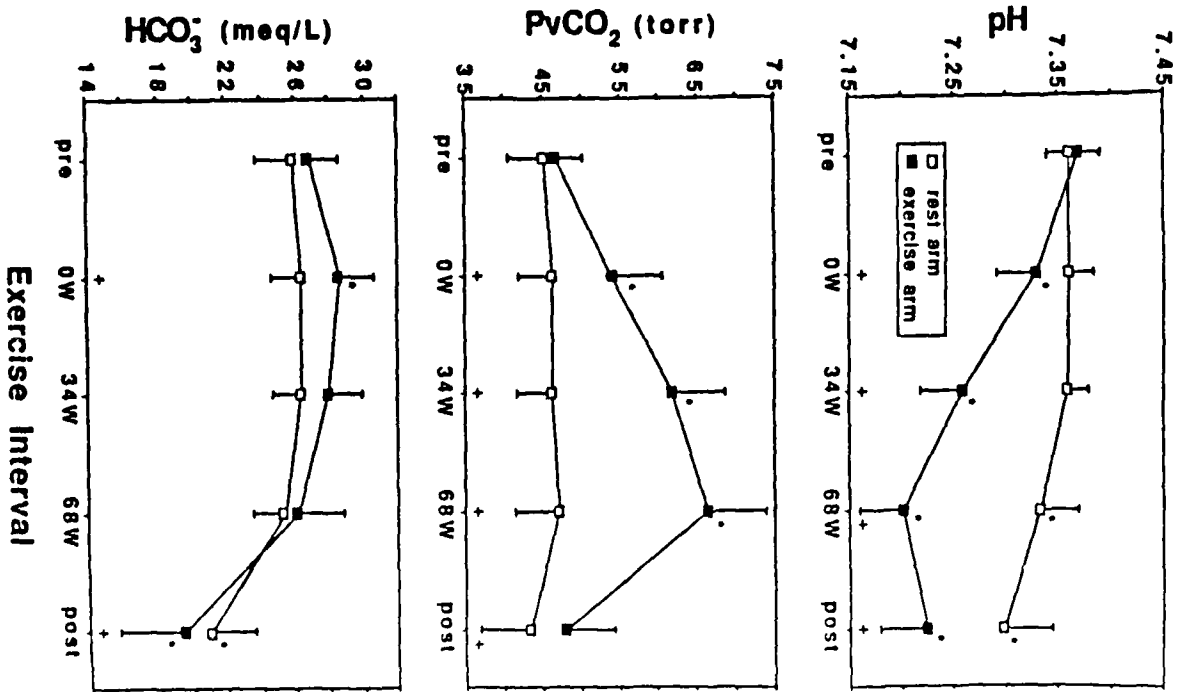


Fig. 2.

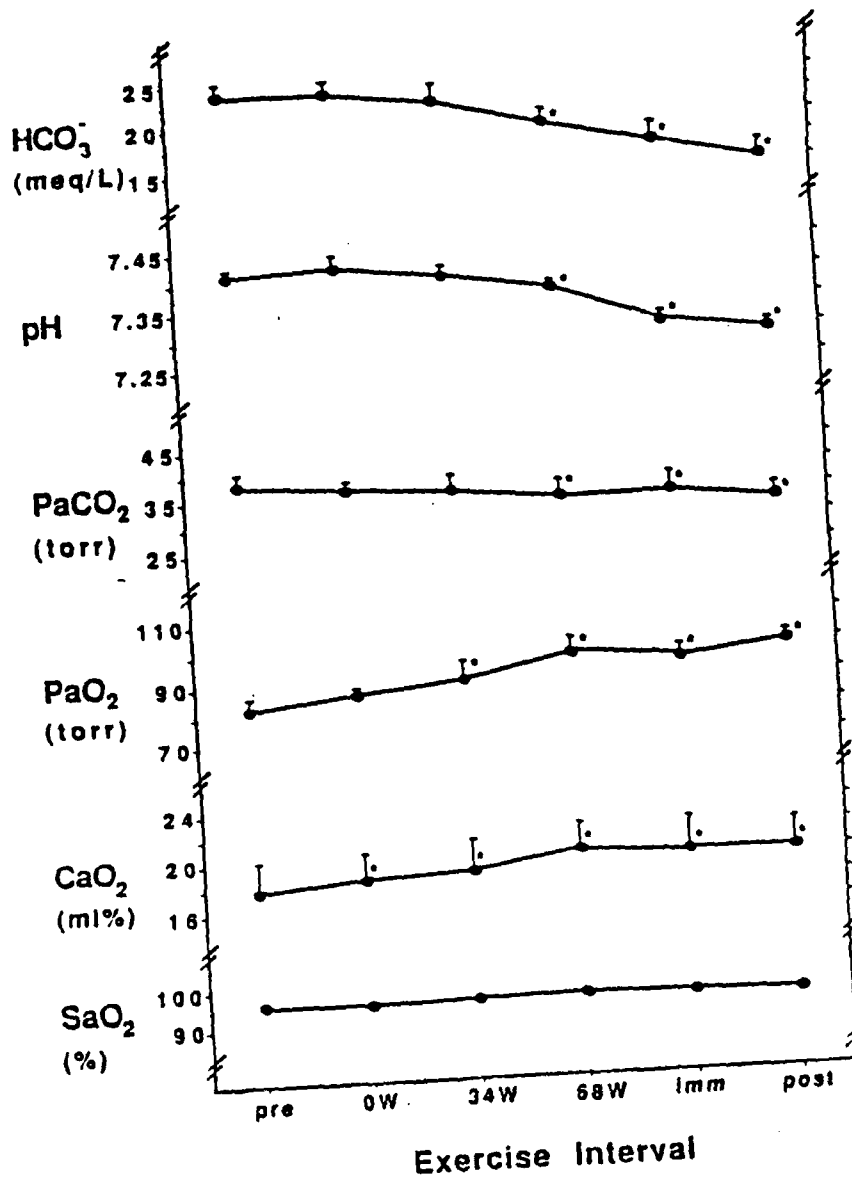


Fig. 3

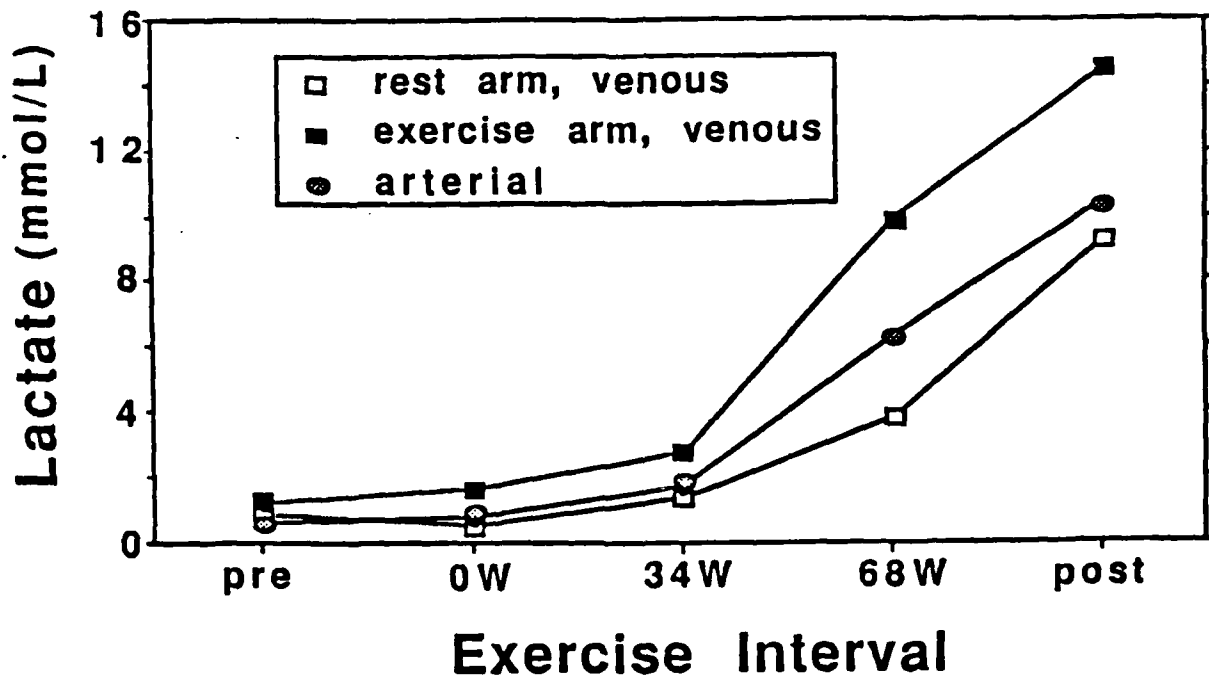


Fig. 4

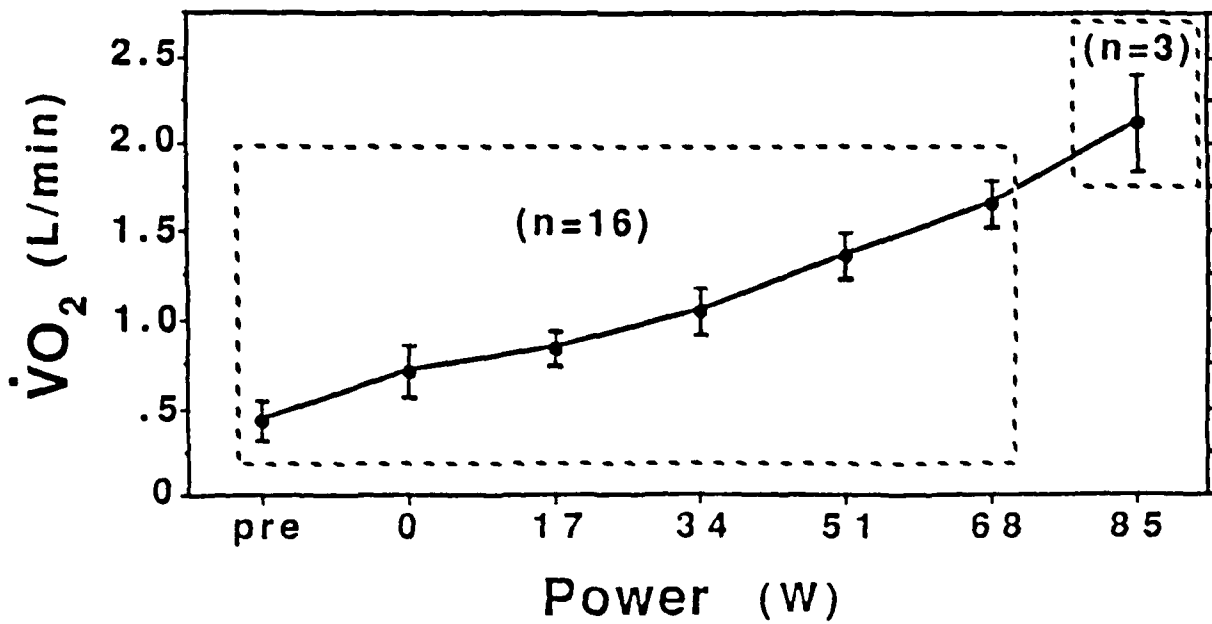


Fig. 5

**Haptoglobin: Poor Indicator of Aerobic Capacity
and Chronic Activity**

ABSTRACT

To determine whether haptoglobin concentration is an indicator of aerobic capacity, we measured haptoglobin levels and peak oxygen uptake in 19 males. Haptoglobin was determined using a nephelometric technique and oxygen uptake was measured during an incremental cycle exercise test. The mean haptoglobin +/- SD was 72 +/- 41 mg/dl while peak oxygen uptake was 3.34+/- .52 L/min or 47.0+/- 5.5 ml/kg/min. The correlation between the measurements was not significant whether oxygen uptake was expressed in L/min ($r=-.07$) or ml/kg/min ($r=.09$). In the second part of the study, we measured haptoglobin concentration in 31 males before and just prior to completion of Army Basic Training. We noted no significant change with training (76 +/- 44 mg/dl vs. 82 +/- 42). At the end of training, there was a wide range of measurements among subjects (9 to 176 mg/dl) despite the preceding 7 weeks of similar activity. We conclude that haptoglobin concentration is a poor index of aerobic capacity and chronic activity.

Index terms: HAPTOGLOBIN, OXYGEN UPTAKE, ANEMIA, HEMOLYSIS

INTRODUCTION

Aged red cells are normally removed from the circulation by the reticuloendothelial system. Occasionally, hemolysis occurs in the intravascular space and hemoglobin is released into the plasma. When this happens, the hemoglobin combines with haptoglobin, a glycoprotein produced by the liver (3). The resulting complex is subsequently removed from the circulation by the hepatocytes (2). Normally, haptoglobin production keeps pace with haptoglobin clearance, but conditions which increase hemolysis can result in abnormally low levels of serum haptoglobin (13).

Strenuous exercise can increase intravascular hemolysis (7,9,11), and decrease haptoglobin concentration (6,8,15,). Regular exercise can also increase plasma volume (16) and possibly dilute plasma constituents. Thus it's not surprising that many athletes have low levels of haptoglobin (11,12,16). In 1984, Spitler et al (17) reported a negative correlation ($r=-.76$, $p<.05$) between haptoglobin concentration and maximum VO₂ in males. They theorized that subjects with a greater aerobic capacity had exercised more and thus had increased hemolysis and lower haptoglobin levels. The investigators then suggested that haptoglobin concentration might serve as an index of physical fitness or chronic activity.

An easily measured index of aerobic capacity or regular exercise would certainly be useful. However, we would expect different methods of training to have a variable effect on haptoglobin concentration and maximal oxygen consumption. Even if training is similar, a relationship could be obscured by genetic and metabolic differences between individuals. In fact, Selby and Eichner (16) recently noted an inconsistent relationship between training distance and haptoglobin level in swimmers. In the present study, we reexamined the relationship between aerobic capacity and haptoglobin concentration. We also determined the usefulness of haptoglobin concentration as an indicator of activity by measuring haptoglobin levels in a number of individuals who had undergone several weeks of similar training.

METHODS

In the first part of the study, we determined the relationship between haptoglobin concentration and peak $\dot{V}O_2$. Nineteen healthy black males, aged 17 to 22, volunteered to participate. All had negative screening tests for sickle cell trait. Their average height \pm SD was 176 \pm 9 cm and their weight was 72 \pm 8 kg. Most exercised regularly but none were considered elite athletes. All were about to undergo Army Basic Training at Fort Bliss, TX. After the study was explained in detail, each volunteer gave written informed consent. All volunteers had a normal medical history and physical exam.

On the day prior to testing, the volunteers completed the in-processing procedures required by the Army. This included short walks and prolonged standing, but no strenuous activity. After a good night's rest, the fasting volunteers reported for testing. Blood was drawn from an antecubital vein for determination of haptoglobin concentration and complete blood count. The subjects then ate a light breakfast and rested for two hours.

We measured peak VO_2 using a 25 watt/minute incremental exercise test to exhaustion on an electronically braked cycle ergometer (KEM 2). During the test, the subject breathed through a two-way mouthpiece. We measured ventilation with a pneumotachometer (Hans Rudolph No. 3800) while respiratory gases were measured at the mouthpiece using a mass spectrometer (Perkin Elmer, MGA 1100). An on-line computer system (Medical Graphics Corporation-2000) was used to calculate VO_2 and other variables breath-by-breath. Peak VO_2 refers to the highest average VO_2 per minute measured during the test.

Haptoglobin levels were determined using rate nephelometry, an approach that measures the increase in scattered light that occurs as haptoglobin-antibody complexes form (Beckman Haptoglobin Reagent in conjunction with a Beckman Immunochemistry

System and CS Calibrator 1). The coefficient of variation for this test is 5%. The complete blood count was measured using an automated hematology analyzer (Technicon H-1).

In the second part of the study, we determined the utility of haptoglobin as an indicator of activity. Another group of 31 healthy black males (age: 22 +/- 3 yr; height: 172 +/- 18 cm; weight: 70 +/- 5 kg), about to undergo Basic Training, volunteered to participate. Blood samples for haptoglobin concentration determination were drawn before training and tested similar to those in the first part of the study. One to three days prior to completion of training, blood samples were again obtained while the subjects were in a fasting state after a night's rest. Training was not reduced on the day prior to measurement.

Basic Training is an eight week regimen that has been shown to increase $\dot{V}O_2$ max by an average of 4% (14). The subjects began training at different times between March and May and completed training between May and July. During basic training, the recruits exercised six days per week. On three of the days (i.e. Monday, Wednesday, and Friday) they did conditioning drills and an 8.5 mph run that progressed from .5 to three miles. On the other three days, the form of exercise was chosen from a group that included combat drills, an obstacle course, and relay races. Although it's unlikely that two subjects had exactly the same

experience, in general, the overall activity level, surface on which the subjects exercised, and footwear were quite similar between subjects.

The data was analyzed using descriptive statistics, Pearson's correlation coefficient, and a paired-t test. Statistical significance was determined at the .05 level.

RESULTS

Values are expressed as mean \pm SD. Peak VO_2 for the 19 subjects in the first part of the study was $3.34 \pm .52$ L/min or 47.0 ± 5.5 ml/kg/min. These values are comparable to those reported by Patton et al (14) for males entering Basic Training. Haptoglobin concentration was 72 ± 41 mg/dl, with a range of 5 to 145 mg/dl. Peak VO_2 (ml/kg/min) is plotted against haptoglobin concentration in figure 1. There was a poor correlation between the measurements irrespective of whether VO_2 was expressed in L/min ($r = -.07$) or ml/kg/min ($r = .09$). The haptoglobin concentration was abnormally low (less than 30 mg/dl) in one subject. His hemoglobin was 15.2 g/dl and his red cell indices were normal. Hemoglobin concentration for the group was 14.4 ± 1.2 g/dl. Four subjects with normal haptoglobin levels had hemoglobin levels below 14 g/dl. All had normal red cell indices and reticulocyte counts.

In the second part of the study, haptoglobin concentration before Basic Training was 75.7 ± 43.5 mg/dl for the 31 subjects. Four of the volunteers had abnormally low haptoglobin concentrations. Of the four, one had an abnormal hemoglobin level (13.2 g/dl) with normal indices. Five other subjects with normal haptoglobin concentration had hemoglobin levels less than 14g/dl. All six had normal red cell indices and reticulocyte counts. After Basic Training, haptoglobin concentration was 82.7 ± 42 mg/dl, which was not significantly different from the measurement before training. The range after training was 9 to 176 mg/dl. Haptoglobin concentration values had increased in 17 subjects and decreased in 14 subjects. Two of the four subjects with low haptoglobin levels before training still had abnormal levels after training, but no one with a normal haptoglobin concentration before training had an abnormal level after training.

DISCUSSION

In the first part of our study we found no relationship between haptoglobin concentration and peak VO_2 in 19 young males. In contrast, Spitler et al (17) reported a negative correlation between the two variables in their males. It's difficult to attribute this discrepancy to a difference in methods or subjects. Both groups used a similar exercise test to determine peak VO_2 and the nephelometric test used to measure haptoglobin

concentration is accurate. Our subjects were younger than Spitler et al's (mean=41yr) and our subjects were black, but the significance of this is uncertain. There was, however, less variation in peak VO₂ among our subjects which would make it more difficult to identify a relationship between peak VO₂ and haptoglobin concentration.

A large proportion of our subjects (10 out of 50) had a low hemoglobin concentration (less than 14 g/dl). This appears to be a common finding in Basic Trainees (1). All ten subjects had normal red cell indices and a normal reticulocyte count, and only one had a low haptoglobin concentration. Therefore, we suspect that the low hemoglobin concentration was caused by a benign process such as training-induced hypervolemia (4). If the four subjects with low hemoglobin levels were excluded from analysis in the first part of the study, there was still no correlation between haptoglobin concentration and peak VO₂. Thus, it's unlikely this explains the difference in results.

Interestingly, Spitler et al also tested a group of females and found no correlation between peak VO₂ and haptoglobin concentration (17). This discrepancy, in conjunction with our results, suggests that haptoglobin concentration may not be related to aerobic capacity. We believe this poor correlation can be explained by the many unrelated and sometimes opposing factors that affect the two measurements (figure 2). For example, Davidson (7) suggested that exercise-induced hemolysis is caused

by mechanical trauma and thus is determined by hardness of the training surface, heaviness of stride, the distance run, and age of the red cells. Although running distance may influence changes in maximum VO_2 , its unlikely that the other factors have a significant effect on anything but intravascular hemolysis and haptoglobin concentration. Variation in those factors among our subjects could therefore account for the poor correlation between peak VO_2 and haptoglobin level.

Unrelated genetic factors may also play a role. A subject endowed with a high aerobic capacity could exercise very little and conceivably have a higher VO_2 and haptoglobin concentration than a poorly endowed subject who trained regularly. Similarly, a subject who exercised regularly but had a genetically determined high rate of haptoglobin production could have a higher haptoglobin concentration than a subject with a low rate of haptoglobin production who did not exercise.

Finally, kinetic differences between haptoglobin metabolism and changes in maximum VO_2 may contribute to the lack of correlation between measurements. Taylor et al (18) demonstrated a 40% decrease in haptoglobin concentration after a single bout of prolonged strenuous exercise. A proportional improvement in peak VO_2 would certainly require more than a single bout of exercise (10). Taylor et al also reported that the haptoglobin concentration returned to base line 24 hours after the bout of exercise. He attributed this rapid increase to an

exercise-induced acute phase response (18). Similarly, Ross and Attwood (15) found that several days of training decreased haptoglobin concentration, but after a day's rest the level returned to base line. A proportional decrease in $\dot{V}O_2$ would surely require longer than 24 hours (5). We believe that these differences in kinetic factors, along with variation in genetic predisposition and training methods, may be responsible for the poor correlation between haptoglobin concentration and aerobic capacity.

In the second part of this study, we saw a wide range of haptoglobin levels among individuals who had undergone over seven weeks of Army Basic Training. During this time, the amount of exercise and other activity were well controlled. The wide variation in haptoglobin concentration, which may have been due to differences in individual technique, haptoglobin metabolism, red cell fragility, etc., suggests that this measurement should not be used to distinguish more active subjects from those less active.

Because we didn't quantitate training activity prior to Basic Training, the second part of this study did not evaluate whether changes in activity affect an individual's haptoglobin concentration. Furthermore, it's uncertain whether changes in haptoglobin concentration within an individual are correlated with changes in $\dot{V}O_2$, since peak $\dot{V}O_2$ was not measured. However, a previous study showed a 4% increase in mean peak $\dot{V}O_2$ after basic

training (14). The lack of change in our present subjects' haptoglobin levels suggests that there may be no correlation with changes in $\dot{V}O_2$. It's also possible that maximal oxygen consumption in our group of subjects did not change or that the haptoglobin measurement is insensitive to small changes in oxygen uptake because the the rate of hemolysis is not significantly affected.

In conclusion, we found a poor correlation between haptoglobin concentration and peak $\dot{V}O_2$. Furthermore, there was a wide range of haptoglobin levels among individuals who had completed over 7 weeks of similar activity. These results suggest that haptoglobin concentration may be a poor indicator of aerobic capacity and chronic activity.

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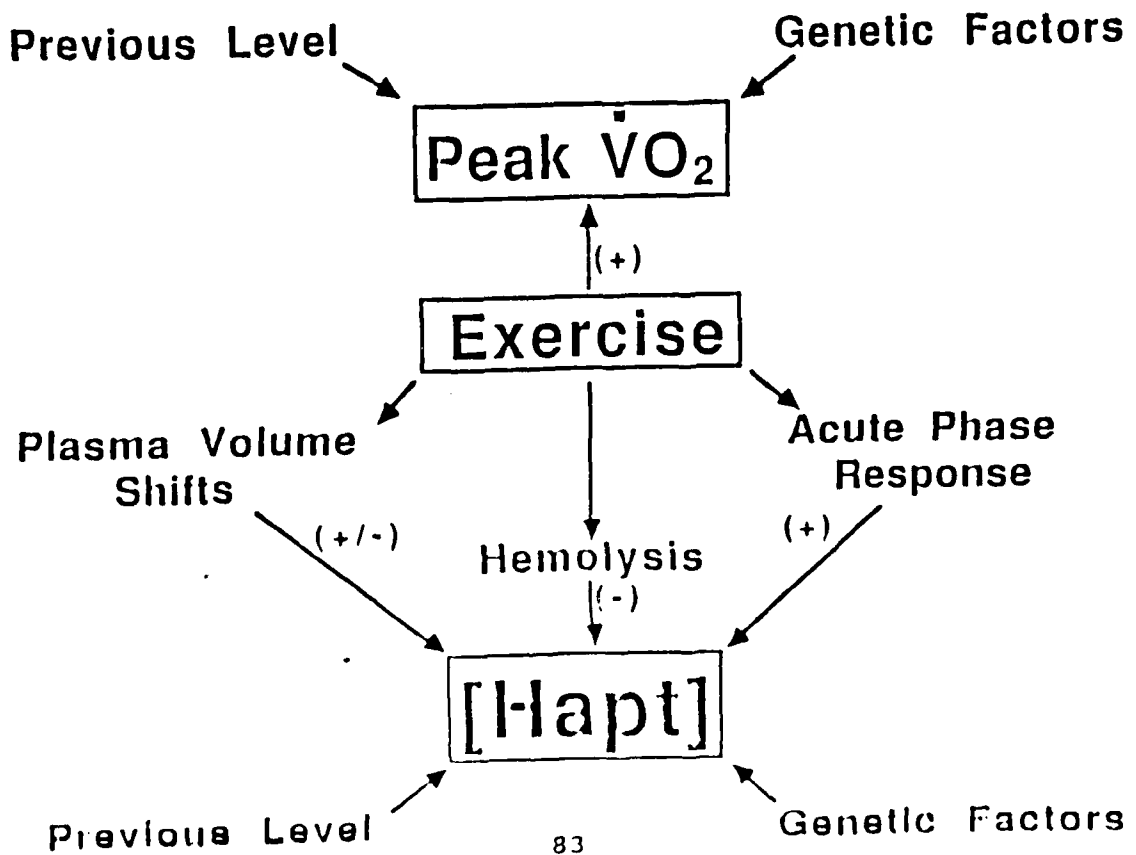
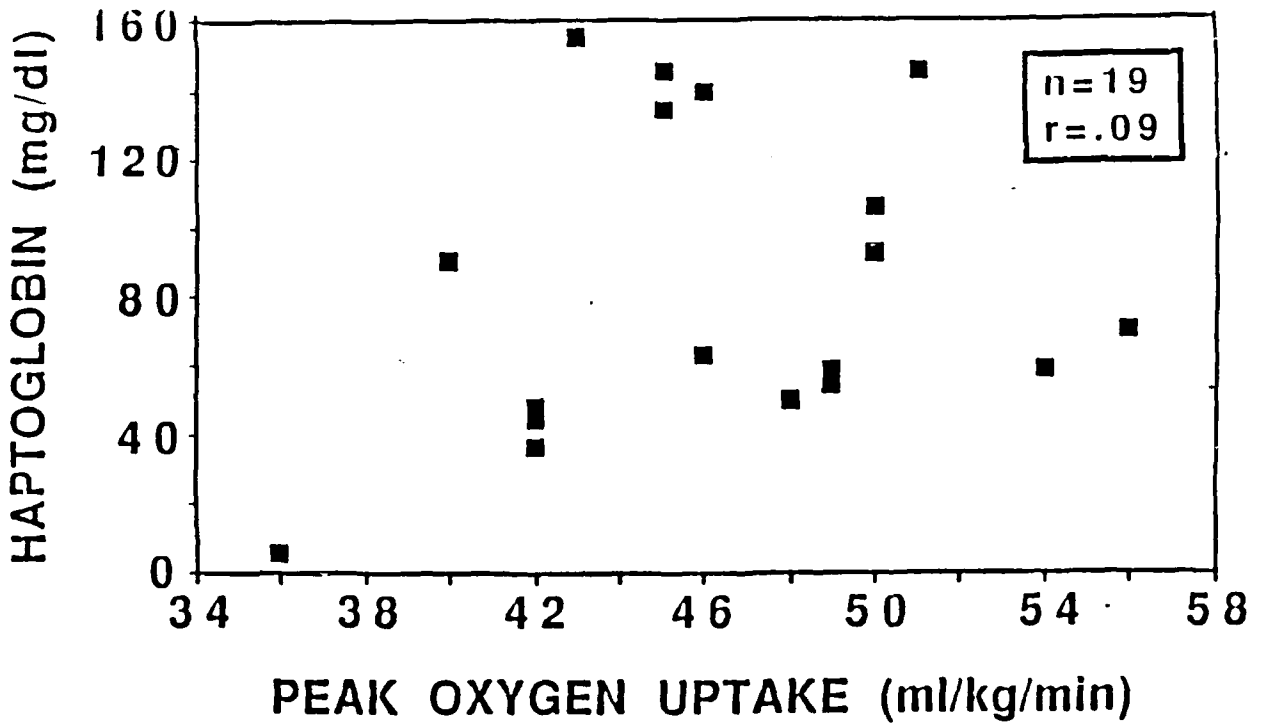
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Figure Legends

Figure 1- Relationship between pre-exercise haptoglobin concentration and peak oxygen uptake during cycle exercise.

Figure 2- Factors which affect peak $\dot{V}O_2$ and haptoglobin concentration (hapt).



GLOSSARY

V_T :	Tidal volume; that volume of air inhaled or exhaled with each breath.
VC:	Vital capacity; the maximum volume of air exhaled from the point of maximum inspiration.
FRC:	Functional residual capacity; the sum of RV and ERV (the volume of air remaining in the lungs at the end-expiratory position). The method of measurement should be indicated as with RV.
TLC:	Total lung capacity; the sum of all volume compartments or the volume of air in the lungs after maximal inspiration. The method of measurement should be indicated, as with RV.
FEV ₁ :	The volume of air exhaled during the first second of the FVC.
Raw:	Airway resistance.
SGaw:	Specific conductance.
MVV:	Maximal voluntary ventilation.
V_D :	The physiologic dead-space volume.
V_D/V_T :	Dead space/tidal volume ratio.
\dot{V}_E :	Expired volume per minute (BTPS).
f:	Respiratory frequency.
$\dot{V}O_2$:	Oxygen consumption per minute (STPD).
$\dot{V}CO_2$:	Carbon dioxide production per minute (STPD).

HR:	Heart rate.
w:	Power in watts.
AT:	Anaerobic threshold.
PaO ₂ :	Arterial oxygen tension.
PaCO ₂ :	Arterial carbon dioxide tension.
SaO ₂ :	Arterial oxygen saturation.
PvO ₂ :	Venous oxygen tension.
PvCO ₂ :	Venous carbon dioxide tension.
pH:	Negative logarithm of the concentration of free hydrogen ions in solution.
P(A-a)O ₂ :	Alveolar-arterial oxygen pressure difference.
P ₅₀ :	Oxygen tension at 50 percent of Hb saturation.
2,3 DPG:	2,3 diphosphoglycerate.
D _L CO _{SB} :	Single breath carbon monoxide diffusing capacity.
D _L CO/V _A :	Diffusing capacity per unit of alveolar volume.

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