THE RELATIONSHIP BETWEEN THE HYPOXIC VENTILATORY RESPONSE AND ARTERIAL DESATURATION DURING HEAVY WORK

by

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ABSTRACT

Arterial desaturation in fit athletes, during exercise at an intensity greater than or equal to 90% of $\dot{V}O_2$ max has been reported by a number of authors yet the etiology of these changes remain obscure. Inadequate pulmonary ventilation due to a blunted respiratory drive, or lung mechanics has been implicated as a factor in the etiology of this phenomenon. It was the purpose of this experiment to investigate the relationship between arterial desaturation and ventilatory response to hypoxia (HVR). Twelve healthy male subjects (age = 23.8 $\pm$ 3.6 yrs., height = 181.6 $\pm$ 5.6 cms., Weight = 73.7 $\pm$ 6.2 kg., $\dot{V}O_2$ max = 63.2 $\pm$ 2.2 ml kg^{-1} min^{-1}) performed a five minute exercise test on a treadmill at 100% of $\dot{V}O_2$ max. Arterial samples for pH, PCO_2, PO_2, and SaO_2 were withdrawn via an indwelling arterial cannula at rest and every 15s throughout the exercise test. The blood gas samples were analyzed with an Instrument Laboratories 1306 blood gas analyzer. Ventilation and $\dot{V}O_2$ were measured by a Beckman metabolic measurement cart. On a separate occasion the ventilatory response to hypoxia (HVR) was determined by recording $\dot{V}E$ as progressive hypoxia was induced by adding N_2 to a mixing chamber. SaO_2 was measured using a Hewlett-Packard ear oximeter; to maintain isocapnia small ammounts of CO_2 were added to the open circuit system. ANOVA for repeated measured was used to evaluate changes in blood gases, ventilation, and $\dot{V}O_2$. Simple linear regression and multiple linear regression was used to evaluate the relationship between the changes in SaO_2 and HVR

and the descriptive variables. Subjects showed a significant decline in arterial saturation and PO_2 over the course of the test ($p < 0.01$, and $p < 0.01$). Four subjects (Mild) exhibited modest decreases in SaO_2 to ($94.6 \pm 1.9\%$), three (Moderate) showed an intermediate response (SaO_2 $91.6 \pm 0.1\%$) and five (Marked) demonstrated a marked decrease in arterial saturation ($SaO_2 = 90.0 \pm 1.2\%$). The differences in PO_2 and SaO_2 between Mild and Marked groups were significant ($p < 0.05$, and $p < 0.01$); there were no significant differences between groups in $\dot{V}E$, $\dot{V}O_2$, pH or PCO_2. There was no significant correlation between the lowest SaO_2 reached and HVR, or any of the descriptive variables. Nine subjects did not reach maximal $\dot{V}E$ (as determined by the $\dot{V}O_2$ max test) on the exercise test, two subjects exhibited similar ventilation, and the remaining subject exceeded maximal $\dot{V}E$, but fell into the Mild group with respect to desaturation. Oxygen uptake exceeded that recorded for the $\dot{V}O_2$ max determination for four of the five subjects in the Marked group; the remaining subjects demonstrated lower or similar values. It was concluded that arterial desaturation was not related to blunted hypoxic drive.

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LIST OF SYMBOLS

FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
2,3-DPG	2,3-diphosphoglycerate
H^+	hydrogen ion
HVR	hypoxic ventilatory response
HCVR	hypercapnic ventilatory response
PCO_2	partial pressure of carbon dioxide
pH	negative logarithm of hydrogen ion concentration
PO_2	partial pressure of oxygen
SaO_2	arterial oxygen saturation
$\dot{V}E$	expired minute ventilation
$\dot{V}O_{2\,max}$	maximal oxygen consumption

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This thesis is dedicated to my parents, Bob and Barbara Hopkins who set the precident for higher education.

INTRODUCTION

In healthy individuals exercising at sea level the pulmonary system is not generally thought to be a limiting factor to performance during maximal aerobic exercise. However, recent research (Dempsey et al., 1984; Powers et al., 1984; Young and Wollcock, 1978; Williams et al., 1986) has demonstrated a decline in arterial oxygen tension of sufficient magnitude to cause desaturation of hemoglobin during maximal exercise tasks. This suggests that the respiratory system may be capable of limiting performance, particularly in individuals capable of very high work outputs. During exercise the combined effect of increasing temperature, decreased pH and alterations in 2,3-DPG, combine to produce a rightward shift in the oxygen hemoglobin dissociation curve, resulting in a decline in saturation from a normal value of 97 to 98% saturated to approximately 94 to 95% saturated (Thompson and Dempsey, 1974). The effect of this rightward shift on O_2 content of blood is minimal at the lung where the partial pressure of oxygen is high. However, at the working muscle where oxygen partial pressures are low, the net effect is increasing release of oxygen, preserving the diffusion gradient into the muscle cell mitochondria (Thompson and Dempsey, 1974).

Arterial desaturation, greater than that expected from the changes described above has been reported during very intense exercise, dating from 1919, when Harrop observed a decline in arterial saturation to 85% immediately following heavy exercise.

in very highly trained individuals with a high aerobic capacity exercising at an exercise intensity greater than 90% of maximal (Dempsey et al., 1984; Powers et al., 1984; Williams et al., 1986).

Maximal oxygen consumption ($\dot{V}O_2$ max), and hence maximal aerobic performance is limited by a number of factors (DiPrampero, 1985). As $\dot{V}O_2$ max is observed to increase with increasing partial pressure of oxygen (Bannister and Cunningham, 1954; Kaisjer, 1970; and others) and with red cell infusion (Buick et al., 1980) and decrease with hypoxia (Squires and Buskirk, 1982; Welsh, 1987 for review) and acute anemia (Woodson et al., 1978), the main limitation to aerobic performance has been considered to be the oxygen transport system. Clearly, other factors such as mitochondrial oxygen utilization, peripheral circulation and oxygen diffusion at the working muscle can also exert some constraint. In two legged exercise, approximately 75% of $\dot{V}O_2$ max is set by oxygen transport with the remaining 25% being equally accounted for by mitochondrial capacity and peripheral diffusion and perfusion (Diprampro, 1985). Thus it can be seen that arterial desaturation leading to decreased oxygen delivery and decreased diffusion gradient at the muscle can significantly effect $\dot{V}O_2$ max. The level of desaturation at which a limit to $\dot{V}O_2$ max can be observed has not been established, although some authors (Squires and Buskirk, 1982) feel that it may be on the order of four percent. In the elite athlete performing at maximal levels any decrement in maximal aerobic performance may be significant.

A variety of mechanisms have been proposed to account for these observations including venoarterial shunting , ventilation perfusion inequality , hypoventilation and diffusion limitation (Powers and Williams, 1987). Current thinking suggests that the latter two explanations may be the most likely. Thus two main issues may be considered :

1. pulmonary ventilation is not adequate either as a result of blunted respiratory drive or of a mechanical inability of the pulmonary system to meet the high levels of ventilation required (Dempsey et al., 1984).
2. pulmonary ventilation is adequate but diffusion of oxygen is limited by shortened red cell transit time or increased diffusion distance due to localized edema at very high levels of pulmonary blood flow (Dempsey et al., 1984; Powers and Williams, 1987).

It has been suggested that the factors determining exercise ventilation represent the integration of the chemical stimulus to breathe with the mechanical constraints imposed by the work of breathing (Dempsey et al., 1985). Both a decrease in exercise ventilation (Martin et al., 1978a; Martin et al., 1979.) and a low hypoxic ventilatory response (Martin et al., 1979) have been demonstrated in endurance athletes compared with non-endurance athletes. Therefore it is logical to consider that if hypoventilation is a factor in arterial desaturation during intense exercise that desaturation may be more likely in those individuals with a blunted response to hypoxia. Thus the purpose of this study was to examine the relationship between the hypoxic ventilatory response and changes in arterial oxygen

saturation in healthy endurance and non-endurance trained athletes during high intensity exercise at sea level.

METHODS

A non-probability sample of 12 healthy male subjects was selected from a total of 16 individuals who volunteered for the study. Criteria for participation included normal cardiovascular and respiratory function, normal arterial circulation to the hand and maximal oxygen consumption ($\dot{V}O_2$ max) $\geq$ 60 ml.kg^{-1}.min^{-1}. Of the sixteen volunteers, three failed to meet the eligibility requirements and in one subject insertion of the arterial catheter was unsuccessful. All subjects gave informed consent and the experiment was approved by the University of British Columbia Committee on Human Experimentation. A total of six elite endurance and six elite non-endurance athletes were recruited. It was predicted that the division of subjects between predominantly endurance and non-endurance sports would give a range of ventilatory responses to hypoxia.

Baseline Data

Descriptive physical characteristics and $\dot{V}O_2$ max were determined for each subject one to two weeks prior to testing. Pulmonary function testing including FVC, % predicted FVC, FEV_1, and peak flow rate, was carried out for each subject using an autospirometer (Minto Medical Science Co. Ltd., model AS-700). Maximal oxygen uptake was determined utilizing a continuous graded treadmill (Quinton 24-72 treadmill) test. The starting speed was 3.08 m.sec^{-1} and this was increased by 0.22 m.sec^{-1} per minute until volitional fatigue. Analysis of expired respiratory gases was performed (Beckman Metabolic Measurement Cart) and

measurements were tabulated every 15 seconds by a Hewlett Packard 3052A data acquisition system . $\dot{V}O_2$ max was determined by the average of the four highest consecutive 15 second measures of oxygen uptake. This result was used to calculate a treadmill velocity which represented 100% of $\dot{V}O_2$ max.

Exercise Test

Subjects were asked to return again approximately one week later having refrained from eating in the last two hours and from exercising in the last 24 hours. The exercise protocol consisted of a five minute treadmill warm-up at 3.08-3.52 $m.sec^{-1}$ followed by a five minute run at a speed that corresponded to 100% of $\dot{V}O_2$ max.

Data Collection

Prior to the exercise test, an indwelling arterial cannula (Arrow, # 20 gauge, or Jelco #22 gauge) was inserted percutaneously in the right radial artery, after infiltration with local anaesthetic (1% Xylocaine Hydrochloride) and using sterile technique. Each subject was checked for adequate collateral circulation via the ulnar artery (Allen's test) before the cannula was inserted. A minimum volume (1.2 cc) extension tube (Cutter) and and two way stopcock (PVB) filled with normal saline was attached. Cannula patency was maintained by frequent flushing with normal saline to which heparin sodium (2000 u/1) had been added. At the onset of sampling the saline was withdrawn and the arterial samples were anaerobically

collected in pre-heparinized plastic syringes. The frequency of sampling (15 s) did not allow for reinfusion of heparin in saline between samples, nor was it required. All cannulas remained patent until the end of the sampling period.

Arterial blood samples were withdrawn immediately prior to the onset of the exercise test and at 15 second intervals after the start of the test for a total of 21 samples. The blood samples were anaerobically capped and maintained on ice until the test session was complete and batch analysis could be performed. Each 2 ml sample was analyzed within 90 minutes of collection using a Instrument Laboratories 1306 automated Blood Gas/ pH Analyzer. This machine was calibrated using a two point calibration prior to batch analysis and one point calibration was automatically peformed after every sample. The samples were analyzed for pH, PCO_2, and PO_2; oxygen saturation (SaO_2) was calculated automatically. The samples were not corrected for temperature as core temperature was not measured during the data collection. Exercise ventilation and expired gas concentration were measured at 15 second intervals by the system described previously for $\dot{V}O_2$ max determination.

The subjects returned a third time and hypoxic ventilatory responses were measured using a modification of the method of Weil et al., (1970). Basically the subjects breathed room air from a mixing chamber (volume = 13.5 l), through a two-way Rudolph valve. Under continuous cardiac monitoring, progressive hypoxia was induced by the addition of 100% nitrogen gas into the mixing chamber. Oxygen saturation was measured via a Hewlett-Packard 47201A ear oximeter and the amount of nitrogen was

increased at one minute intervals until an oxygen saturation of 80% was reached. End tidal PCO_2 was measured (Beckman LB-2) and isocapnia was maintained $\pm$ 2 torr by the addition of very small amounts of 100% CO_2 gas distal to the mixing chamber. Ventilation was measured via a low resistance pneumotach and and the data was recorded and tabulated every 15 seconds via an IBM data accquisition system. A BMDP P:1R, simple linear regression, program was used to determine the slope of the linear relationship between SaO_2 and ventilation. Subjects were tested until isocapnia was maintained within the range specified above and until 70% of the variation in ventilation could be explained on the basis of changes in SaO_2 ($R^2 \geq 0.7$) or until consistant values were obtained.

Statistical Analysis

BMDP statistical software, P:2V, ANOVA for repeated measures was used to statistically test changes in blood gas parameters, ventilation, and $\dot{V}O_2$ over time. P:1R, Simple Linear Regression, and P:2R, Multiple Linear Regression were used to determine the relationship between changes in SaO_2 and descriptive variables, including HVR.

RESULTS

Baseline Measures

Mean values for the physiologic characteristics of the twelve subjects are reported in Table I . Pulmonary function results were within normal limits for all subjects.

TABLE I. PHYSIOLOGICAL CHARACTERISTICS

	Means ± S.D.
AGE (yrs)	23.8 ± 3.6
HEIGHT (cms)	181.6 ± 5.6
WEIGHT (Kg)	73.7 ± 6.2
$\dot{V}O_2$ max ($ml.kg^{-1}.min^{-1}$)	63.2 ± 2.2

The subjects included two triathletes, three long distance runners (10 km, marathon), two oarsmen (one collegiate and one Olympic medalist), three middle distance runners (400, 800 m), one competitive cyclist and one member of Canada's Pan-Am field hockey team. All subjects were actively training for their respective sports at the time of the investigation.

Changes in Arterial Blood Gases With Exercise

Eleven of the twelve subjects completed the full five minutes of exercise. The remaining subject was unable to complete the full testing time and terminated the test after four minutes and fifteen seconds. The data from this subject were excluded from statistical analysis, but were retained for descriptive purposes. Means and standard deviations for the 15 second

interval measures of pH, PCO_2, PO_2 and SaO_2 in the eleven subjects who completed the full test are reported in Table II.

Resting values for pH, PCO_2, PO_2, and SaO_2, were within normal limits for all subjects. As would be expected from intense exercise a significant ($F = 141$, $p < 0.001$) metabolic acidosis occured; pH declined from a resting value of 7.43 ± 0.03 to 7.21 ± 0.06 at the end of five minutes of exercise. Averaged over all subjects there was a significant decline in PO_2 ($F = 26.1$, $p < 0.001$) and SaO_2 ($F = 64.8$, $p < 0.001$). Subjects fell into three groups with respect to changes in PO_2 and SaO_2; further analysis was directed towards characterizing differences between these groups. As only three subjects fell into the group of intermediate (Moderate) responders, Figures 1 and 2 report data from Mild and Marked groups only. Four subjects (Mild) showed little decline in PO_2 and O_2 saturation, with resting values of PO_2 at 105.8 ± 12.6 torr (SaO_2 $98.2 \pm 0.6\%$) declining to 87.5 ± 5.7 torr (SaO_2 $94.6 \pm 1.9\%$) after the five minute exercise task. Three subjects (Moderate) demonstrated an intermediate decline in PO_2 and SaO_2, with resting PO_2 102.5 ± 3.5 (SaO_2 $98.2 \pm 0.1\%$) declining to 76.5 ± 2.1 torr (SaO_2 $91.6 \pm 0.1\%$). The remaining five subjects (Marked) demonstrated a marked decline in saturation with resting PO_2 declining from 111.0 ± 8.9 torr (SaO_2 $98.5 \pm 0.4\%$) to 71.4 ± 3.5 torr (SaO_2 $90.1 \pm 1.2\%$). ANOVA for mixed model design was used to determine differences between mild and marked groups for PO_2, SaO_2, pH, PCO_2, $\dot{V}O_2$, and $\dot{V}E$. The results of these statistical analyses are presented in Table III. As would be expected during intense exercise, averaged over all

TABLE II

15 SECOND INTERVAL MEASURES FOR ARTERIAL BLOOD VALUES, $\dot{V}O_2$, AND VENTILATION FOR ALL SUBJECTS:

(Mean ± SD.)

TIME (min)	R	0:15	0:30	0:45	1:00	1:15	1:30	1:45	2:00	2:15	2:30	2:45	3:00	3:15	3:30	3:45	4:00	4:15	*4:30	*4:45	*5:00
pH	7.43	7.45	7.45	7.43	7.42	7.40	7.37	7.36	7.34	7.33	7.32	7.31	7.29	7.28	7.27	7.25	7.25	7.25	7.23	7.23	7.21
	0.03	0.02	0.02	0.02	0.03	0.03	0.03	0.03	0.03	0.03	0.04	0.04	0.04	0.05	0.05	0.05	0.05	0.06	0.05	0.06	0.06
PCO2 (torr)	36.3	35.9	37.8	37.3	38.1	38.4	38.3	38.6	38.5	38.0	38.2	38.0	37.4	37.5	38.4	36.9	37.2	36.9	36.6	36.2	36.4
	4.3	3.5	2.7	2.5	2.0	2.7	2.0	2.2	2.2	2.3	2.8	2.1	2.5	2.2	2.6	2.5	2.6	2.6	3.0	2.7	3.3
PO2 (torr)	107	112	102	93	89	89	89	89	88	86	85	83	83	82	81	82	80	79	79	78	78
	9.2	14.4	11.5	8.9	7.5	7.8	6.8	9.0	8.6	9.3	9.2	9.2	10.1	9.0	9.6	9.9	9.6	7.5	8.5	7.5	8.6
SaO2 (%)	98.3	98.4	98.0	97.2	96.9	96.8	96.6	96.3	96.0	95.9	95.3	94.9	94.6	94.3	93.7	93.8	93.1	92.8	92.6	92.3	92.0
	0.44	0.9	0.9	1.0	0.9	0.9	0.9	1.2	1.2	1.4	1.3	1.5	1.6	1.7	2.1	2.1	2.2	1.9	2.2	2.2	2.5
$\dot{V}O_2$(l/min)	-	1.53	2.36	3.78	4.13	4.08	4.17	4.27	4.29	4.29	4.31	4.38	4.41	4.31	4.44	4.50	4.57	4.44	4.61	4.56	4.43
		0.56	0.51	0.62	0.48	0.43	0.39	0.46	0.48	0.39	0.50	0.45	0.44	0.34	0.49	0.42	0.42	0.51	0.44	0.43	0.51
$\dot{V}E$(l/min BTPS)	-	57.8	78.4	102.1	115.2	120.9	127.5	134.5	139.2	138.2	141.2	143.7	143.9	142.6	145.3	145.7	148.0	145.8	149.8	149.1	148.0
		19.5	16.5	20.5	21.3	18.4	17.1	17.6	18.9	18.2	18.6	17.8	16.7	17.6	17.4	17.0	13.0	17.4	15.3	13.6	17.3

* N = 11 subjects

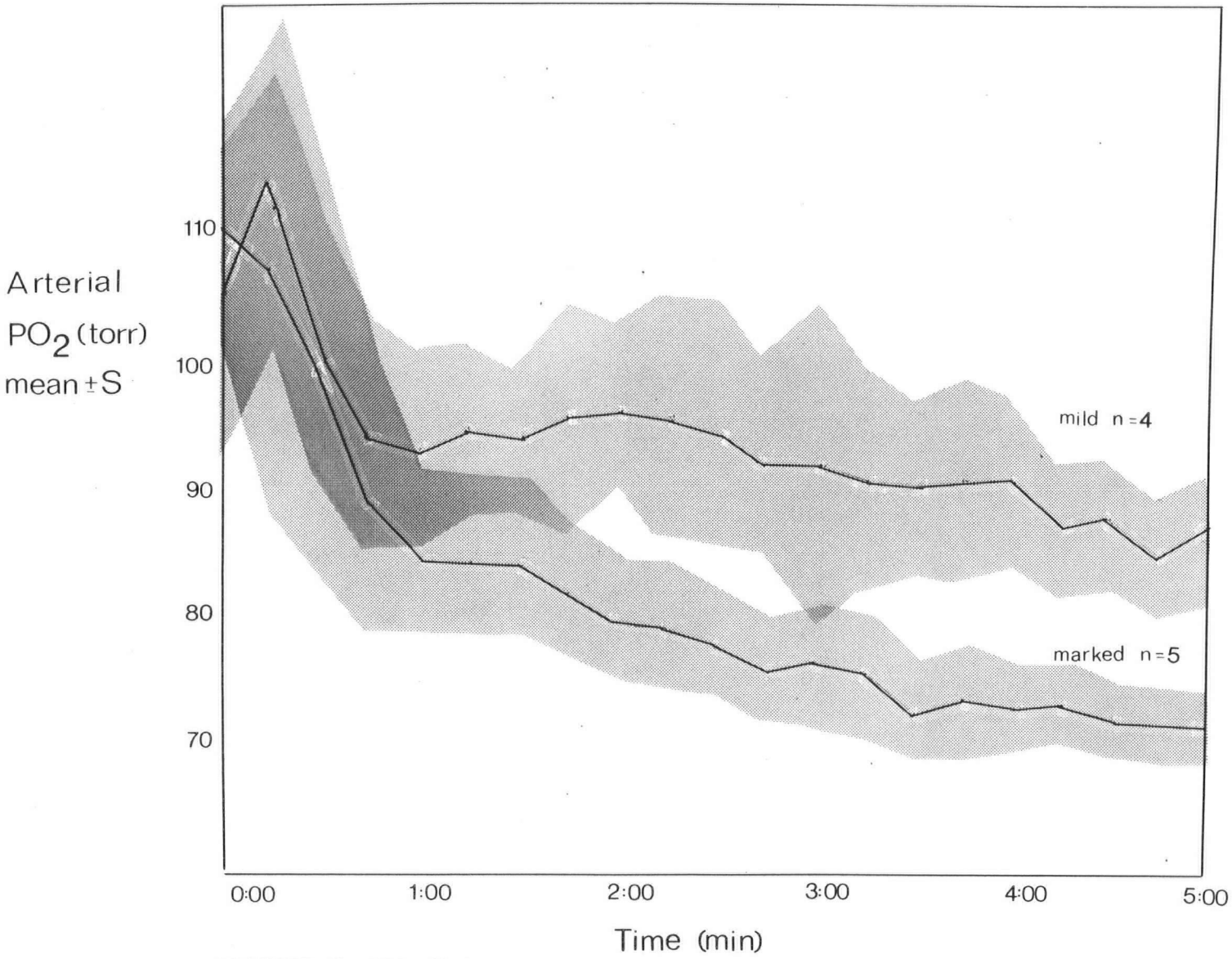

FIGURE 2 CHANGES IN PO_2 OVER TIME

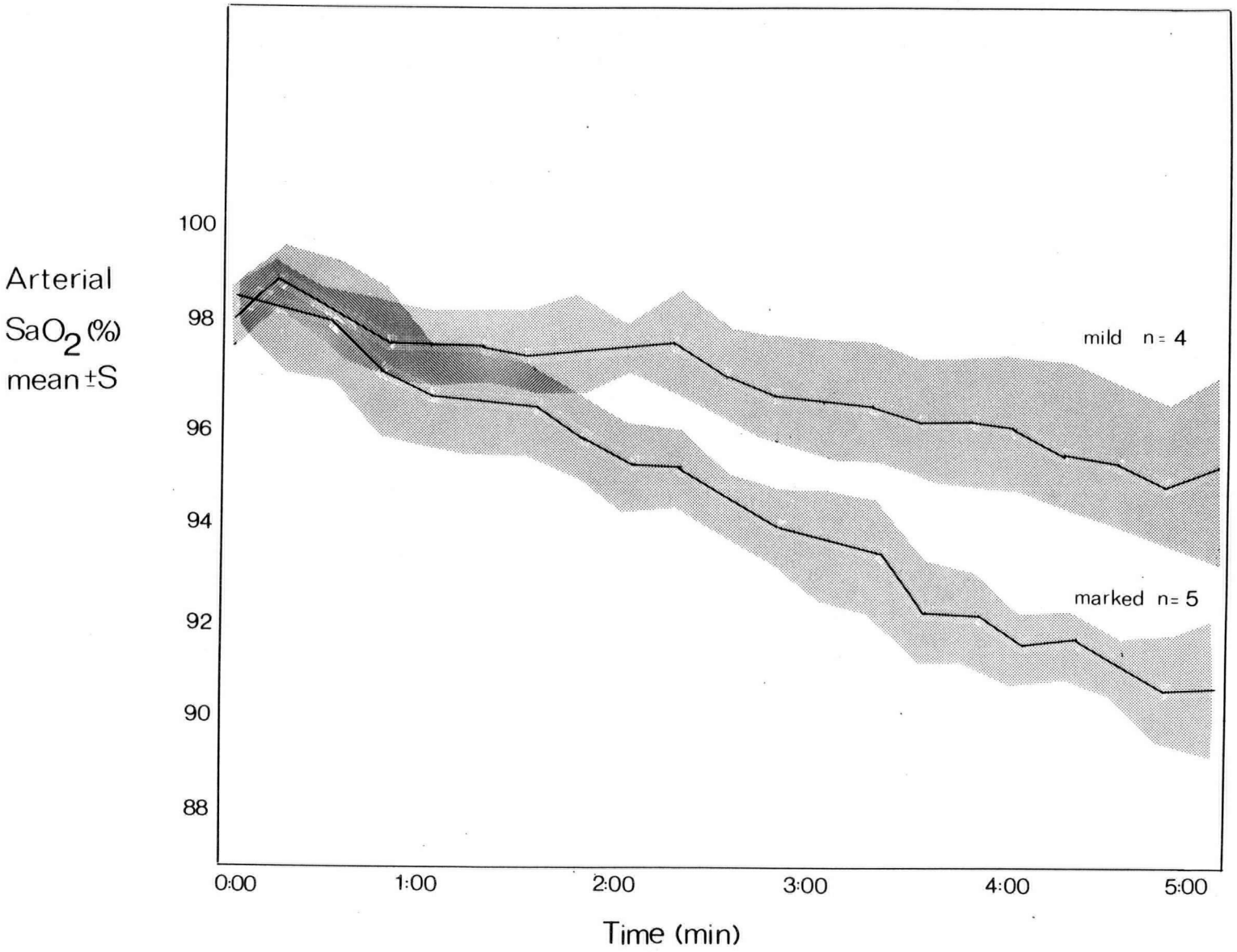

FIGURE 2 CHANGES IN SaO_2 OVER TIME

subjects, there were significant differences in all variables over time. The group by time interaction, which reflects the degree to which both groups exhibited the same change over time revealed significant differences for PO_2 and SaO_2. Values for these two measures were similar for both groups until one minute, then the Marked group demonstrated a steeper rate of decline in PO_2 than the Mild group. There were no significant differences between groups for pH, PCO_2, $\dot{V}E$, and $\dot{V}O_2$.

TABLE III. ANOVA RESULTS

VARIABLE	GROUP F(p)	TIME F(p)	GROUP x TIME F(p)
PO_2	10.1 (<0.05)	22.4 (<0.001)	2.7 (<0.001)
SaO_2	20.1 (<0.01)	64.8 (<0.001)	9.8 (<0.001)
pH	1.0 (>0.05)	96.0 (<0.001)	<1.0
PCO_2	<1.0	2.1 (<0.01)	1.1 (>0.05)
$\dot{V}E$	1.1 (>0.05)	91.4 (<0.001)	<1.0
$\dot{V}O_2$	<1.0	83.2 (<0.001)	<1.0

Changes in $\dot{V}E$ and $\dot{V}O_2$

Fifteen second recordings for $\dot{V}E$ and $\dot{V}O_2$ for the twelve subjects are presented in Table II. Maximal ventilation and VO_2 during the the five minute exercise test are contrasted with values obtained during the $\dot{V}O_2$ max determination in Table III. It can be seen that nine of the twelve subjects achieved higher ventilation during the $\dot{V}O_2$ max determination than during the five minute test. In two, the ventilation was simliar on the two tests and in one subject peak ventilation was higher during the five

minute exercise test. Four subjects achieved higher $\dot{V}O_2$ on the five minute exercise test than on the $\dot{V}O_2$ max determination. These individuals all fell into the marked group with respect to desaturation.

TABLE IV DIFFERENCES IN VENTILATION AND MAXIMAL OXYGEN UPTAKE BETWEEN $\dot{V}O_2$ MAX DETERMINATION AND FIVE MINUTE EXERCISE TEST

GROUP	SUBJECT	OXYGEN CONSUMPTION (liters/min)			VENTILATION (liters/min BTPS)		
		$\dot{V}O_2MAX$	5 min	%	$\dot{V}E_{max}$	$\dot{V}E$ 5min	%
MILD	1.	4.78	4.78	100.0	186.4	169.0	90.7
	2.	4.58	4.18	91.3	127.2	140.8	111.0
	3.	4.46	4.12	92.4	166.0	135.8	81.8
	4.	4.99	4.67	93.6	178.2	140.5	78.8
MOD	5.	4.51	4.30	95.3	145.1	142.0	97.9
	6.	4.13	4.11	99.5	142.4	132.0*	92.7
	7.	5.17	5.08	98.3	148.2	149.3	100.7
MARKED	8.	4.39	4.01	92.7	158.2	143.1	90.4
	9.	5.45	5.51	101.1	191.8	182.7	95.2
	10.	4.10	4.32	105.3	148.6	151.9	102.2
	11.	4.58	4.82	105.2	162.7	154.9	98.0
	12.	4.54	4.60	101.3	143.2	137.9	96.3

* obtained at 4:15

Hypoxic ventilatory response

The measured hypoxic ventilatory response and sport for each subject is recorded in Table V. There appeared to be two distinct groups within our sample of subjects. Six subjects were classified as normal (N) responders and six as having a diminished response (B). Division into these groups was based on analysis of data published by Fleetham et al., (1980); Grindlay-Moore et al., (1982); Rebuck and Campbell, (1974) and Rebuck and Woodley,(1975). The mean slope of the line described by change in ventilation per 1% change in SaO_2 was found to be 1.08 $l.min^{-1}$ .1%

ΔSaO_2^{-1} ; standard deviation was 0.97 1.min^{-1} .1% ΔSaO_2^{-1} reflecting the positively skewed distribution of values.

TABLE V HVR AND SPORT FOR EACH SUBJECT (n = 12)

SUBJECT	SPORT	HVR ($\Delta \dot{V}E/1\%\Delta SaO2$) (1.min^{-1} 1%$\Delta$SaO2)	N or B
1.	Field hockey	0.43	B
2.	400 m, 800 m	0.43	B
3.	rowing	0.78	N
4.	800 m	1.12	N
5.	marathon	1.05	N
6.	marathon	1.03	N
7.	triathlon	0.22	B
8.	400 m	0.22	B
9.	rowing	1.22	N
10.	triathon	0.87	N
11.	10 k	0.43	B
12.	cycling	0.26	B

	MEAN (1.min^{-1} .1%$\Delta SaO2^{-1}$) $\pm$ S.D.
normal	1.02$\pm$0.15
diminished	0.33$\pm$0.10
all	0.67$\pm$0.36

Relationship of HVR to arterial desaturation

Correlation analysis was performed to determine the relationship between the hypoxic ventilatory response and the lowest observed SaO_2. This analysis yielded a correlation coefficient of 0.06, which was non-significant ($F<1.0$). A multiple regression analysis revealed no significant relationship between the degree of arterial desaturation and the dependant variables age, height, weight, $\dot{V}O_2$ max, or treadmill speed of each subject.

DISCUSSION

Arterial desaturation occured to some extent in all of the subjects tested. The traditional view of changes in blood gas parameters during exercise has held that PO_2 is relatively stable and alterations during intense exercise are of insufficient magnitude to cause desaturation of hemoglobin. The small changes observed in the literature (decline to 94-98% saturated) have been attributed to the combined effects of decreasing pH, increasing temperature (Thompson and Dempsey, 1974) and alterations in 2,3-DPG (Klein et al., 1980).

Arterial desaturation has been reported as early as 1919 (Harrop, 1919), but was generally ignored by the scientific community, possibly because of difficulty in obtaining arterial samples during maximal exercise or because of the preponderance of evidence obtained during less intense exercise, which does not demonstrate any changes in PCO_2 or PO_2 (Bjurstedt and Wigertz,1971; O-Barr et al., 1964; Suskind et al., 1950).

Perhaps the most complete study investigating changes in PO_2 and SaO_2 is found in the work of Dempsey et al., (1984). In this study, sixteen endurance athletes, capable of sustaining very high metabolic rates ($\dot{V}O_2$ max = 72±2 ml.kg^{-1}.min^{-1}) performed a progressive exercise test to maximum on a treadmill. Hemoglobin saturation was measured by means of an ear oximeter, and arterial pH, PCO_2, and PO_2 were measured by means of an indwelling arterial cannula. It was found that eight of the sixteen subjects demonstrated a decrease in arterial oxygen content of 21-35 torr, to an PO_2 of less than 75 torr. The most severe hypoxemia was

associated with little or no alveolar hyperventilation. When helium breathing was used to reduce turbulent flow and thus unload the respiratory muscles exercise ventilation increased substantially.

The mechanisms accounting for arterial desaturation during heavy work have not been elucidated, however speculation as to the possible causes considers the following areas: 1. veno-arterial shunt. 2. ventilation-perfusion inequality. 3. diffusion limitation 4. hypoventilation.

Veno-arterial shunt: At rest in the healthy individual small (approximately 1-1.5% of cardiac output (Bachofen et al., 1973)) volumes of blood are shunted via the thebesian veins and bronchial venous blood supply directly into the systemic circuation and therefore do not participate in gas exchange. The introduction of this poorly oxygenated blood results in a small decline in oxygen tension in arterial blood. If shunting were the cause of the decline in PO_2 no change would be expected in oxygen tension with the introduction of a hyperoxic gas mixture. In fact this is not the case, as reports exist of hyperoxia correcting the hypoxemia seen during exercise at sea level (Dempsey et al., 1984; Gale et al., 1985; Torre-Bueno et al., 1985) and at altitude (Gale et al., 1985; Torre-Bueno et al., 1985). Thus some other mechanism must account for this phenomena.

Ventilation-perfusion inequality: Generally ventilation and perfusion of the lung are non-uniform: due to the effects of gravity the base of the lung receives a greater blood flow than does the apex. If ventilation and perfusion inequality increased during maximal exercise then arterial hypoxemia would also

increase as blood passed through a poorly ventilated segment of the lung. During low intensity exercise there is an increase in both apical ventilation and perfusion with the overall result tending to greater homogenity within different areas of the lung. At more intense levels of exercise only minor changes in ventilation-perfusion inequality have been found (Gale et al., 1985) which are not sufficient in magnitude to account for the changes in PO_2 seen during maximal exercise.

Diffusion limitation: Another possible etiology of arterial hypoxemia during heavy exercise relates to diffusion limitation. In the sedentary individual during heavy exercise the transit time for the red blood cell through the pulmonary circulation is well within the time required for complete equilibration (about 0.25 seconds). In the athlete capable of reaching very high work levels, mean transit time may be reduced to 0.40 seconds or less, secondary to increases in pulmonary blood flow. If the blood is also directed to underventilated areas of the lung, transit times may be further reduced to less than 0.25 seconds (Dempsey et al., 1982). Diffusion distance could also be increased if high intravascular pressures within the pulmonary capillary lead to fluid leak and an increase in fluid in the interstitial space. Thus diffusion limitation may also explain the changes in arterial saturation observed (Dempsey et al., 1982).

Hypoventilation: That hypoventilation plays a role in the genesis of arterial hypoxemia seems likely, but to what extent is uncertain. In the study of Dempsey et al., (1984), the

individuals demonstrating the greatest degree of arterial hypoxemia exhibited the lowest ventilatory response to exercise.

Our data indicate that our subjects were well-trained individuals engaged in high level competition. Their mean $\dot{V}O_2$ max is lower than that reported for subjects in some desaturation studies (Dempsey et al., 1984; Williams et al., 1986) but is higher than that reported in studies using less elite athletes (Thompson and Dempsey, 1974). The blood gas data indicates that this was a difficult exercise task to perform; our subjects incurred a significant metabolic acidosis with the average end of exercise pH for the eleven subjects who completed the full five minute test recorded at 7.21 ± 0.06. The subject who was unable to complete the test obtained a pH of 7.13.

An increase in pH was observed in ten of twelve subjects during the first thirty seconds of exercise. This corresponded to a relative hyperventilation as PO_2 levels increased for the first 15 seconds. Changes in PCO_2 (see Table II) were variable and did not correlate with the pH change ($R^2 = 0.05$). It is possible that the increase in pH may reflect the consumption of a hydrogen ion within the working muscle during the hydrolysis of creatinine phosphate, a buffering process which has resulted in alkalosis within the working muscle (Hultman and Sahlin, 1980). Similar changes have been reported by other investigators during exercise of similar intensity (Dempsey et al., 1984.) however these changes were attributed to declines in PCO_2.

The greatest decline in PO_2 occured within the first 45 to 60 seconds of exercise, which corresponded to the period of greatest rise in $\dot{V}O_2$ and $\dot{V}E$ (see Table II). Changes were similar

for all subjects for the first 45 seconds, then those in the Mild group showed some leveling while subjects in the Marked group showed a greater rate of decline (Figure 1). Similar observations were true of the changes on SaO_2 (Figure 2), however both the Mild and Marked groups continued to show a decline in saturation reflecting the effects of increasing acidosis on the oxygen-hemoglobin dissociation curve. Our results are in agreement with those of Dempsey et al., (1984) who showed similar patterns of decline in PO_2 and SaO_2. The mean saturation at the end of five minutes for all subjects, ($91.9 \pm 0.6\%$) is also close to the final saturation observed ($92.0 \pm 2.5\%$) in this study. Another study (Williams et al., 1986) demonstrated greater declines in saturation to $87.0 \pm 0.2\%$ in trained subjects and $92.6 \pm 0.7\%$ in untrained subjects. These values were obtained using an ear oximeter (Biox II), and thus unreliability of this method of data collection may account for observed differences in SaO_2 (Smythe et al., 1986).

Temperature measurements were not made in our subjects and therefore it is likely that the degree of desaturation is underestimated in our subjects. Assuming a rise in temperature of one degree celcius the expected decrease in saturation would be in the order of 0.5%. This is relatively small compared to the decreases as a result of hypoxemia and acidosis.

Arterial desaturation has been shown to be more likely in individuals capable of very high work outputs (Dempsey et al., 1984; Powers and Williams, 1987), exercising at greater than 90% of $\dot{V}O_2$ max. $\dot{V}O_2$, $\dot{V}E$, pH, and PCO_2 were similar between Mild,

Moderate and Marked desaturation groups, therefore the differences in final SaO_2 canot be explained on the basis of differences in fitness or differing work intensity in the group who showed the greatest decline in saturation.

Generally our subjects showed little respiratory compensation for the metabolic acidosis of exercise. In most subjects the resting sample which was taken just prior to the onset of exercise showed a depressed PCO_2 (mean = 36.0±4.4 torr). This is not surprising as the samples were taken as the subject was straddling the treadmill with the mouthpiece for measuring expired gas in place. PCO_2 then increased to a mean value of 37-38 torr and declined to less than 37 torr only in the last minute of exercise. The changes in PCO_2 are less than that reported by Dempsey et al., (1984), even when hyperventilation prior to the onset of exercise was considered. Dempsey et al.,(1984) felt that the relative hypoventilation secondary to mechanical constraint in their subjects might have contributed to arterial desaturation and the lack of compensation for the respiratory acidosis of exercise. Preliminary evidence for this was given by data obtained during studies involving the replacement of room air with helium-oxygen mixtures. This led to an increase in the ventilation and partial correction of the blood gas abnormalities (Dempsey et al., 1984). This possibility does not seem likely in our subjects since nine of the twelve subjects showed greater $\dot{V}E$ on the $\dot{V}O_2$ max determination than on the five minute exercise test. One subject exhibited greater ventilation on the five minute exercise test than the $\dot{V}O_2$ max determination, but fell into the Mild group with respect to desaturation. The remaining

subjects had similar ventilation in both situations; one was in the Moderate group , the other was in the Marked group. It is possible that secondary modifiers of exercise ventilation such as temperature and cathecholamine production (Wasserman et al., 1981) may have contributed to the increased ventilation in the $\dot{V}O_2$ max determination for the majority of the subjects. Certainly it would seem that in this instance that mechanical factors per se, are not significant.

It is possible that respiratory muscle oxygen consumption (Bye et al., 1983) may be responsible for the limited respiratory compensation for the metabolic acidosis during heavy exercise. At ventilations greater than 100 $l.min^{-1}$ the $\dot{V}O_2$ of respiratory muscle ($\dot{V}O_2$ resp) has been estimated to be 2-8 ml O_2 .1 $\dot{V}E^{-1}$ (McKerrow and Otis, 1956; Bradley and Leith, 1978). Therefore in our subjects whose mean peak ventilation was 149.8 $l.min^{-1}$, $\dot{V}O_2$ resp could range from 0.3 to 1.2 $l.min^{-1}$, representing 6 to 26% of $\dot{V}O_2$ max. It has been argued that the critical ventilation where any increase in $\dot{V}O_2$ would go entirely to respiratory muscles is 140 $l.min^{-1}$ (Otis, 1954). Our subjects exceeded this level of ventilation, thus it may be that optimum ventilation is limited due to oxygen delivery.

The amount of lactate produced by respiratory muscles is not trivial, and a similar arguement can be applied to CO_2 excretion and respiratory compensation. Assuming no lactate consumption and distribution throughout body water, lactate production from respiratory muscle could reach as high as 10 $mmol.l^{-1}$ (Roussos, 1982). It is possible that at maximal exercise,particularly in a

situation where oxygen delivery may be constrained, a situation could be reached where any increase in ventilation to increase CO_2 excretion would be balanced by an increase in respiratory muscle lactate production leading in an increasing acidosis. Thus it may be that the level of ventilation reached during maximal exercise may represent an optimum ventilation, balancing O_2 delivery to the working muscle and respiratory compensation for the acidosis of exercise with the increasing metabolic demands of the respiratory muscles.

The mean hypoxic ventilatory response for our subjects (0.67 ± 0.36 $l.min^{-1}.1\%\Delta SaO_2^{-1}$) is less than that reported for the normal population (1.09 ± 0.97 $l.min^{-1}.1\%\Delta SaO_2^{-1}$; Fleetham et al., 1980; Grindley-Moore et al 1984; Rebuck et al., 1976; Rebuck and Woodley, 1975) and possibly reflects the lower HVR reported for athletic individuals (Byrne -Quinn et al., 1982; Mather et al., 1982; Martin et al., 1978b). The curve of the normal population is not bell-shaped but is positively skewed . While all our values fell within the normal range of values expected for the general population it was apparent that there were two distinct responses to hypoxia. Six subjects (N) showed HVRs that were close to the mean reported for the normal population above, while six subjects (B) showed responses that were approximately one third of those values (N = 1.02 ± 0.15 $l.min^{-1}.1\%\Delta SaO_2^{-1}$ vs B = 0.33 ± 0.10 $l.min^{-1}.1\%\Delta SaO_2^{-1}$). There was no relationship between sport and HVR. That is, in our subjects who were similar in $\dot{V}O_2$ max, there was no difference between endurance trained (mean HVR = 0.64 ± 0.35 $l.min^{-1}.1\%\Delta SaO_2^{-1}$) and non-endurance trained (mean HVR = 0.70 ± 0.37 $l.min^{-1}.1\%\Delta SaO_2^{-1}$) athletes. In this analysis the

two oarsmen were considered to be non-endurance athletes since the race distance is 2000m and takes approximately 6 minutes to complete. At the time of testing (May) these athletes were in specific training for this event. This data is in contrast to Martin et al., (1979), who found blunted HVRs in endurance trained athletes compared to a control group of non-endurance athletes and non athletic normals. In these subjects $\dot{V}O_2$ max was significantly higher in the endurance athletes than non-endurance athletes and non-athletes and differences in fitness may account for the differences between groups.

Since endurance athletes have a lower exercise ventilation at any given work intensity, (Martin et al., 1979; Martin et al., 1978a; Martin et al., 1978b; Stockley, 1978) and exercise ventilation is related to HVR (Martin et al., 1978b; Stockley, 1978), it was predicted that that hypoventilation secondary to blunted respiratory drives might be cause of the arterial desaturation. It then would be expected that some evidence of blunted response to hypoxia would be evident in our subjects. The advantage to the individual of being able to "ignore" hypoxemia would be a reduction in respiratory work, and possibly a more efficient pattern of ventilation. This was not observed in our subjects; there was no significant relationship between HVR and lowest SaO_2 reached. Thus it seems unlikely that blunted respiratory drive plays a role in the desaturation seen in these individuals.

The remaining possibility to be considered is diffusion limitation and there is some indirect evidence to support this as

a mechanism for the arterial desaturation observed in our subjects. Eight subjects did not reach $\dot{V}O_2$ max on the five minute exercise test. With one exception these subjects fell into the Mild or Moderate group with respect to arterial desaturation. Of the subjects who developed marked desaturation four of the five scored higher scores for $\dot{V}O_2$ on the five minute exercise test than on their $\dot{V}O_2$ max determination. This difference ranged from 1.1 to 5.0 percent increase. Although speculative, the only logical explanation for this increase is that a greater cardiac output was achieved by these subjects due to decreased peripheral pooling of blood. This would be expected since the duration of the exercise test was much less than during the $\dot{V}O_2$ max determination (13-18 minutes). Thus subjects would have less peripheral pooling of blood due to thermoregulation during the five minute test and greater venous return. Since limits to $\dot{V}O_2$ max can be considered to be about 75% due to limitations oxygen transport (DiPrampero, 1984) any increase in cardiac output would be expected to increase $\dot{V}O_2$ max. If diffusion limitation due to shortened red cell transit time were the cause of arterial desaturation, any factor which increased cardiac output and therefore shortened transit time, would be expected to result in a increase in arterial desaturation. If the changes in cardiac output were considered to be the cause of the increase in $\dot{V}O_2$ it could also explain the observed changes in SaO_2 in four of the five subjects who developed marked desaturation.

In summary arterial desaturation was observed in all of our subjects ranging from Mild (SaO_2 = 94.6%), Moderate (91.6%) to Marked (90.1%). There was no differences between groups in $\dot{V}E$,

$\dot{V}O_2$ max, pH and PCO_2, and it seems unlikely that mechanical factors limiting ventilation are significant since only two subjects approached or exceeded maximal ventilation determined during the $\dot{V}O_2$ max test. There was no relationship between the degree of desaturation and hypoxic ventilatory response. Indirect evidence suggests that diffusion limitation due to shortened red cell transit time is the most likely explanation for this phenomena.

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APPENDIX A
REVIEW OF LITERATURE

VENTILATION DURING EXERCISE

The ventilatory response to muscular exercise is commonly described in three phases. In phase I a rapid increase occurs, beginning before any metabolite of muscular work could reach a known area of chemoreception. The extent that $\dot{V}E$ increases with the first breath varies from almost no change up to 100% of the steady state response. In animals, this is accompanied by an increase in PO_2 and decrease in PCO_2; thus it is argued that the initial increase in ventilation cannot reflect the action of hydrogen ion at the chemoreceptor (Whipp, 1978). The use of neural blocking agents in animals has demonstrated as much as a fifty percent decrease in ventilatory response to hindlimb motion when afferent fibers are blocked suggesting that the likely source of neurogenic drive to exercise ventilation is the small myelinated and nonmyelinated fibers. The evidence surrounding this issue is conflicting as similar studies in man have demonstrated that ventilation is independant of hindlimb motion and varies with metabolic rate (Wasserman et al., 1981).

Following this initial increase there is a slow rise (phase II) in ventilation until steady state (phase III) is reached. Because of the delay in phase II response following the onset of exercise this is generally thought to be consistant with the transit of some mediator to the chemoreceptors (Whipp, 1978). The total ventilation seen in steady state is then the summation of

the humoral and continuing neurogenic stimuli. Exercise ventilation has been demonstrated to be linearly related to the minute ventilation of carbon dioxide; CO_2 and H^+ are generally considered to be the ongoing humoral stimuli to exercise ventilation (Favier et al., 1983). Of interest is work in individuals who have undergone carotid body resection. Phase I ventilation does not appear to be significantly altered in these individuals, however they demonstrate an increase in VE during phase II ventilation during exercise that is approximately one half that of normal controls. They also demonstrate a lower arterial pH secondary to the inability of these subjects to develop respiratory compensation for the metabolic acidosis of exercise. This evidence suggests that the carotid body chemoreception is intimately related to exercise ventilation (Wasserman et al., 1975).

This neurohumoral theory of exercise ventilatory control accounts for the ventilatory responses during muscular exercise by suggesting that there is first a rapid neurogenic component, followed by a slower humoral component. Included in the neurogenic component are imputs from the cerebral cortex, including voluntary imputs, and from muscle spindles and joint proprioceptor afferents. Humoral mechanisms suggested include CO_2 flow to the lungs, alterations in intramedullary and CSF $[H^+]$, increase in pulmonary blood flow, and oscillations of PCO_2 about an unchanged mean. Secondary factors affecting exercise ventilation are body temperature which would appear to be a slowly developing modifier of primary stimuli and circulating cathecholamines which may provide additional drive to

hyperventilate (Whipp, 1978).

The rise in ventilation during exercise correlates with both the ventilatory response to hypoxia as well as the ventilatory response to hypercapnia (Martin et al., 1979; Stockley et al., 1978). Thus the endurance athlete with a documented blunting of these responses could be expected to have a lower exercise ventilation for any given level of exercise. This has been consistantly documented in the literature (Martin et al., 1978a; Martin et al., 1979) and an inverse relationship has been found between VO_2 and the ventilatory response to exercise (Morrison et al., 1973). The use of pressure volume curves to calculate the work of breathing, has demonstrated the physiologic advantage of a low exercise ventilation (Milic-Emili et al., 1962). Subjects who exhibit a decreased exercise ventilation will perform less respiratory work, and therefore experience less dyspnea. As dyspnea is a powerful limitation to physical work, it reasonable to expect that a more efficient ventilatory pattern would facilitate athletic performance.

RESPIRATORY DRIVES

The hypoxic ventilatory response

The hypoxic ventilatory response is a measure of the sensitivity of the cortical and peripheral regulating centers to hypoxic stress. The investigation of the HVR involves a circuit where PO_2 and PCO_2 can be controlled. The concentration of oxygen is gradually lowered in this circuit by the addition of nitrogen until alveolar oxygen tension is lowered to 40 torr (Collins et al., 1978; Hirshman et al., 1975; Scoggin et al., 1978; Schoene

et al., 1982) which corresponds to a hemoglobin saturation of about 80%. Changes in the alveolar partial pressure of carbon dioxide secondary to hyperventilation, are prevented by the addition of carbon dioxide in small quantities to the gas mixture. Arterial oxygen saturation is monitored by means of an ear oximeter. The minute ventilation is then recorded in the supine subject and comparison of minute ventilation versus partial pressure of oxygen or percent saturation of hemoglobin (SaO_2) is made. Due to the "S" shaped nature of the oxygen hemoglobin dissociation curve, the graph of SaO_2 versus minute ventilation ($\dot{V}E$) is a linear function, in which the slope of the line varies as a function of an individual's sensitivity to hypoxia (Tammling, 1983). The graph of $\dot{V}E$ versus PaO_2 is a curve which is described by the hyperbolic function $\dot{V}E = Vo + A/(PAO_2 - 32)$, where $\dot{V}E$ is the observed ventilation (BTPS), PAO_2 is alveolar oxygen tension in torr and Vo is the extrapolated asymptote. The A value describes the shape of the curve, with a high A value denoting a brisk ventilatory response to hypoxia and a low A value a blunted response to hypoxia (Collins et al., 1978). Statistical analysis of several studies (Bryne-Quinn et al., 1971; Collins et al., 1978; Hirshman et al., 1975; Grindlay-Moore et al., 1974;) indicate a skewed distribution toward lower values of A mith a mean A value of 145 and standard deviation equal to 80. Similar analysis of studies comparing $\dot{V}E$ to SaO_2 (Fleetham et al., 1980; Grindlay-Moore et al., 1984; Rebuck and Campbell 1975; Rebuck and Woodley 1975; Rebuck et al., 1976) indicates a similar skewed distribution with the mean slope equal

to 1.09 ± 0.97 $l.min^{-1}$. $1\%\Delta Sa0_2^{-1}$. When the hypoxic ventilatory response is measured under conditions where the CO_2 tension is allowed to fall (poikilocapnic hypoxia) the observed response is less than under conditions where carbon dioxide tension remains constant (isocapnic hypoxia). This reflects the inhibitory effect of decreasing CO_2 on ventilation (Grindley-Moore et al., 1984).

Some interesting observations have come to light regarding the ventilatory response to hypoxia in different athletic groups. Elite mountaineers capable of attaining the extremes of altitude have been found to have a greatly enhanced ventilatory response to hypoxia compared with normal controls while elite middle and long distance runners show a blunted response (Bryne-Quinn et al., 1971; Collins et al., 1978; Martin et al., 1979, Schoene et al., 1982). In one series, climbers were found to have an A value of 158.9 ± 29.9 (mean$\pm$ S.D.), while the corresponding value for runners was 49.3 ± 7.1. Normal controls exhibited a value of 109.9 ± 21.0 (Schoene et al., 1982).

Some intriguing questions are raised as to whether the hypoxic ventilatory response is a genetic or acquired trait. Cross sectional studies suggest that the former is true. Elite endurance athletes show a blunting of HVR that is reflected in the responses of first degree relatives who are not engaged in the same activities (Collins et al., 1978). This would suggest that the observed differences in the climber vs endurance runner population represents selection in these groups; the climber who is successful at altitude because of an ability to climb high without succumbing to altitude illness and the runner who is able

to run fast because of decreased exercise ventilation, less respiratory work and less dyspnea. It is interesting to note that the ventilatory response to hypoxia is blunted in high altitude residents as well as endurance runners.

Hypercapnic ventilatory response

The sensitivity of an individual to carbon dioxide can be measured by maintaining a constant PO_2 and increasing the concentration of carbon dioxide in the rebreathing circuit. The graph of $\dot{V}E$ versus PCO_2 is a linear function the slope of which varies as a function of individual sensitivity to hypercapnia. A wide range of responses to CO_2 is seen among normal individuals (Read, 1966; Irsigler, 1976) with women tending to be lower responders then men. The mean slope of the response line has been reported to be 2.60 $l.min^{-1}.torr^{-1}$ increase in PCO_2 with a standard deviation of 1.2 $l.min^{-1}.torr^{-1}$ (Irgsiler, 1976). Since individual variability is so great, it may be more reasonable to consider CO_2 response in terms of low (<1.5 $l.min^{-1}.torr^{-1}$), medium (1.5-5.0 $l.min^{-1}.torr^{-1}$), and high (>5.0 $l.min^{-1}.torr^{-1}$) responders.

RESPIRATORY FACTORS LIMITING PERFORMANCE

It was not until recently that the pulmonary system has been considered to exert some constraint on maximal exercise performance in some individuals. Several authors have demonstrated a decline in arterial oxygen saturation with intense exercise which offers evidence to encourage this line of thought. There are three possible mechanisms by which the respiratory

system could limit maximal exercise performance (Bye, 1984; Dempsey, 1986; Dempsey and Fregosi, 1985; Dempsey et al., 1982): 1. lung mechanics. 2. energetics and 3. respiratory muscle fatigue.

Lung mechanics: In normal individuals performing moderate exercise, the tidal flow volume loop falls well within the maximal flow volume loop, however, in maximal exercise, the limits of this maximal flow volume loop may be approached or exceeded (Olafson and Hyatt, 1969). These limits are reached on the expiratory side where flow becomes independent of effort (Hyatt, 1983) thus exceeding the maximal volumes could be expected to lead to hyperinflation of the lungs resulting in shortening of the inspiratory muscles and increased elastic work of breathing.

Energetics: In a situation where oxygen transport is limited, such as at maximal exercise, it is possible that any increase in respiratory muscle $\dot{V}O_2$ ($\dot{V}O_2$ resp) would decrease the available oxygen for non-respiratory muscles. At low levels of ventilation, the portion of $\dot{V}O_2$ supplying respiratory muscles is relatively low. At levels of exercise, ventilation greater than 100 $l.min^{-1}$, $\dot{V}O_2$ resp may be as great as 2-8 $ml\ O_2.l^{-1}\ \dot{V}E$ (McKerrow and Otis, 1956). Some authors have argued that it is possible to reach a state where any increase in $\dot{V}O_2$ would be consumed entirely by the respiratory muscles (Otis, 1954).

Respiratory muscle fatigue: Respiratory muscle fatigue can be defined as the failure of the respiratory muscles to generate the force to produce a given pleural pressure. For the diaphragm, this occurs with pressures that are 40% of maximum

pressure while, for the inspiratory muscles, fatigue results if the pleural pressure required is greater than 50 - 70% of maximum (Bye, 1983). The unique characteristics of diaphragm muscle, with ability to maintain very high oxidative capacity, renders this muscle relatively resistant to fatigue compared with skeletal muscle (Wasserman et al., 1981) However, several studies have shown that high levels of ventilation cannot be maintained indefinitely (Bender and Martin, 1985; Bye et al., 1984; Martin et al., 1981). A decline in the strength of the ventilatory muscles at the end of a marathon race with a fall in maximum inspiratory and expiratory mouth pressures and transdiaphragmatic pressures suggests that these considerations may be of practical concern (Loke et al., 1982). Reduced time to exhaustion has been shown during short-term maximal exercise after 150 minutes of maximal ventilation (Martin et al., 1982). This reduced exhaustion time occurred at a significantly lower heart rate and ventilatory rate than during the control situation where this ventilatory work was not performed.

Ventilatory endurance has been shown to be greater in athletes than non-athletes despite identical energy costs of breathing for the two groups investigated (Martin et al., 1981). Training studies have shown an increase in MVV and the percentage of MVV that can be sustained for 15 minutes of voluntary hyperventilation in subjects involved in an endurance training program when compared to strength training individuals and control subjects (Leith and Bradley, 1976). This suggests that ventilatory muscle training may occur during endurance exercise

training.

HYPOXEMIA DURING EXERCISE

Hypoxia and altitude

Conventional wisdom has held that the athlete with normal lungs is exposed to hypoxia under normal circumstances only with travel to high altitude. It has become apparent that hypoxemia of sufficient magnitude to cause desaturation of hemoglobin can be found in healthy athletes exercising near maximal levels at sea level (Dempsey et al., 1984; Powers et al., 1984; Williams et al., 1986; and others). Hypoxia is the main stimulus to the physiologic alterations seen at high altitude. An increase in minute ventilation precedes other changes, and is mediated through medullary chemorespiratory centres and through the carotid body system. This in turn acts to decrease arterial PCO_2 which acts on peripheral chemoreceptors and to decrease minute ventilation. Thus the net ventilation observed at high altitude is the sum of two conflicting stimuli. Hypoxia has been shown to be an important pulmonary vasoconstrictor during normal regulatory responses. At sea level, this protects against perfusion of hypoventilated segment of lung, however, at high altitude, the changes are more generalized, leading to pulmonary hypertension. In the cerebral circulation, hypoxia acts as a vasodilator, a protective mechanism which optimises oxygen delivery in a situation of decreased supply. This effect is countered in part by the effects of the accompanying hypocapnia which acts as a vasoconstrictor of the cerebral vasculature (Sutton and Grey, 1982). The implications of these changes are

important considerations in the pathogenesis of altitude sickness.

Altitude illness

Many investigators believe the underlying pathologic mechanisms of the different altitude illnesses to be the same. Generally, altitude illness is thought to result from a disorder of water handling. Exposure to altitude leads to a shift of fluid from the intravascular space to the interstitial space. In the lung, this is augmented by the increase in intravascular pressure secondary to the hypoxia-mediated vasoconstriction. In the brain, an increased cerebral blood flow secondary to the vasodilatory effects of hypoxia leads to increased filtration of fluid and edema formation according to Starling's law. It can therefore be appreciated that the individual who exhibits relative hypoventilation at altitude will have a greater degree of hypoxia and hypercapnia, leading to increased vasodilation and an exageration of the pathologic mechanisms described above (Sutton and Grey, 1983).

This line of thought suggests that a brisk ventilatory response to hypoxia should offer some protection against the development of the altitude illnesses. Several studies support this reasoning. It has been found that the incidence of Acute Mountain Sickness (AMS) is greater in those individuals who have the greatest increase in minute ventilation (Anholm et al., 1979). In climbers to extreme altitude, it was found that the individuals who were able to climb the highest and sleep at the highest altitude, had an exagerated response to hypoxia (Schoene

et al., 1982). This suggests that those individuals with a brisk response to hypoxia optimise their oxygen uptake in an environment where oxygen is limited and maintain a low arterial and alveolar PCO_2. The advantages of this are threefold: firstly, a decrease in alveolar carbon dioxide allows a relative increase in the alveolar partial pressure of oxygen. Secondly, the respiratory alkalosis facilitates the binding of oxygen to hemoglobin, thus a higher protion of hemoglobin is saturated for a given PO_2. Thirdly, a lower carbon dioxide tension minimises the vasodilatory effects of hypoxia.

Exercise in a hypoxic environment

Performance increases linearly with increasing PO_2 and drops off sharply with decreasing PO_2 (see Welsh, 1987 for review). In mild hypoxia (inspired PO_2 120 torr) the changes are small and not statistically significant, however, at higher altitudes increasing desaturation of hemoglobin is found particularly with exercise (Squires and Buskirk, 1982). Maximal oxygen oxygen uptake is related to oxygen delivery, (cardiac output and oxygen-hemoglobin dissociation curve) peripheral blood flow and diffusion gradient for oxygen, and the ability of the mitochondria to utilize oxygen (DiPrampero, 1985). Thus the arterial desaturation seen at altitude limits $\dot{V}O_2$ max by limiting the diffusion of oxygen into the muscle cell. The effects of hypoxia on oxygen delivery are complex, however, as blood flow to active muscle is affected by arterial oxygen tension (Hogan and Welsh, 1986). During submaximal exercise, no effect is seen on $\dot{V}O_2$ unless hypoxemia is severe (Welsh, 1987). During acute

exposure, little effect is seen on cardiac output during maximal exercise, although vasodilation is seen in active beds (Welsh 1987). $\dot{V}E$ is increased for submaximal exercise and little or no change is seen during maximal exercise. An increase in pH is observed during submaximal exercise reflecting the effect of hypoxia on pulmonary ventilation (Welsh, 1987).

HEMOGLOBIN AFFINITY FOR OXYGEN DURING EXERCISE

During exercise, the combined effects of decreased pH, increased temperature and alterations in 2,3 DPG serve to produce a right shift in the hemoglobin-oxygen (HbO_2) dissociation curve. Generally, this change is relatively minor, such that hemoglobin remains highly saturated with oxygen (94-98%). This change facilitates increased oxygen delivery to tissues at low oxygen tensions; during exercise in the normoxic condition, the decreased binding in the lungs is more than offset by the increase in O_2 delivery at the tissues. During hypoxic exercise, eventually the point is reached where any gain in tissue delivery is balanced by loss in oxygen loading at the lungs.

A pH decrease from 7.4 to 7.2 will cause a decrease in SaO_2 from 97% to approximately 94% saturated at a PO_2 of 90 torr. Similarly, an increase in temperature from 37 ^{o}C to 38 ^{o}C will cause a decrease in SaO_2 from 97% to 96.4% (see Appendix B). During exercise, the combined effects of temperature and pH are additive (Thompson and Dempsey, 1984).

2,3-Diphosphoglycerate (2,3-DPG) is an inorganic phosphate that acts in the red cell to alter its oxygen carrying capacity in the following ways: 1. 2,3-DPG binds directly to hemoglobin,

combining more readily to deoxyhemoglobin and tending to hold it in this state. 2. When synthesised inside the red cell, this molecule is unable to cross the red cell membrane. This alters the Donnan equilibrium and acts to decrease intracellular pH and thus alter the HbO_2 curve through effect on pH (Kloche, 1972). Short-term exhaustive exercise has been show to produce a change in hemoglobin affinity for oxygen independent of temperature and pH, that can be attributed to changes in 2,3-DPG. Very intense exercise is required to produce these changes; approximately 30-50% of the variability in saturation can be accounted for by alteration in 2,3-DPG (Klein et al., 1980).

Another adaptive mechanism that occurs during exercise is an increase in oxygen carrying capacity as a result of small changes in hemoglobin concentration. The hemoconcentration seen accounts for an increase of 1.0-1.5 g hemoglobin per 100 ml leading to an increase in oxygen content of the order of about 2 ml per 100 ml (Thompson and Dempsey, 1974). In addition, changes in NA^+, K^+, and Cl^- ions have been documented (Kloche, 1972) which may contribute to the changes in arterial saturation during exercise.

ARTERIAL DESATURATION DURING HEAVY EXERCISE

The documentation of arterial desaturation during heavy work is not new (Harrop, 1919), however, this phenomena was ignored aside from scattered reports (Rowell et al., 1964; Thompson and Dempsey, 1974) until recently. The most likely explanation for this lack of interest in the part of the scientific community was the focus on arterial gas data obtained during submaximal exercise (Bjursted and Wigertz, 1971; O-Barr et al., 1964;

Suskind et al., 1950) which did not show any decline in hemoglobin saturation that could not be accounted for by the factors previously discussed. Perhaps the most complete study investigating changes in PO_2 and SaO_2 is found in the work of Dempsey et al., 1984. In his study, sixteen endurance athletes capable of sustaining very high metabolic rates ($\dot{V}O_2$ max = 72±2 $ml.kg^{-1} min^{-1}$) performed a progressive exercise test on a treadmill. Hemoglobin saturation was measured by means of an ear oximeter, and arterial pH, PCO_2, and PO_2 were measured by means of an indwelling arterial cannula. It was found that eight of the sixten subjects demonstrated a decrease in arterial oxygen content of 21-35 torr, to a PO_2 of less than 75 torr. The most severe hypoxemia was associated with little or no alveolar hyperventilation. When helium breathing was used to reduce turbulent flow, and thus unload the respiratory muscles, exercise ventilation increased substantially.

The mechanisms accounting for arterial desaturation during heavy work have not been elucidated, however, the speculation as to possible causes proceeds along the following lines: 1. veno-arterial shunt. 2. ventilation-perfusion inequality. 3. diffusion limitation. 4. hypoventilation.

Venoarterial shunt: At rest in the healthy individual, there are small (approximately 1-1.5% of cardiac output (Bachofen et al., 1973) amounts of blood that are shunted via the thebesbian veins and bronchial venous blood supply directly into the systemic circulation and therefore do not participate in gas exchange. The introduction of this poorly oxygenated blood

causes a small decline in oxygen tension in arterial blood. If shunting were the cause of the decline in PO_2, no change would be expected in oxygen tension with the introduction of a hyperoxic gas mixture. In fact, this is not the case with reports of hyperoxia correcting the hypoxia seen during exercise at sea level (Dempsey et al., 1984; Gale et al., 1985; Torre-Bueno et al., 1985). Thus some other mechanism must account for this phenomena.

Ventilation-perfusion inequality: Generally ventilation and perfusion of the lung are non-uniform: due to the effects of gravity the bases of the lung recieve a greater blood flow than do the apices. If ventilation and perfusion inequality increased then arterial hypoxemia could also increase as blood passed through a poorly ventilated segment of the lung. During low intensity exercise there is an increase in both apical ventilation and perfusion with the overall result tending to greater homogenity within different areas of the lung. At more intense levels of exercise only minor changes in ventilation-perfusion unequality have been found (Gale et al., 1985) which are not sufficient to account for the changes in $P O_2$ seen during maximal exercise.

Diffusion limitation: Another possible etiology of arterial hypoxemia during heavy exercise relates to diffusion limitation. In the sedentary individual during heavy exercise the transit time for the red blood cell through the pulmonary circulation is well the time required for complete equilibration (about 0.25 seconds). In the athlete capable of reaching very high work levels, mean transit time may be reduced to 0.40 seconds or less,

secondary to increases in pulmonary blood flow. If the blood is also directed to underventilated areas of the lung, transit times may be further reduced to less than 0.25 second (Dempsey et al., 1982). Diffusion distance could also be increased if high intravascular pressures within the pulmonary capillary lead to fluid leak and an increase in fluid in the interstitial space. Thus diffusion limitation may also explain the changes in arterial saturation observed.

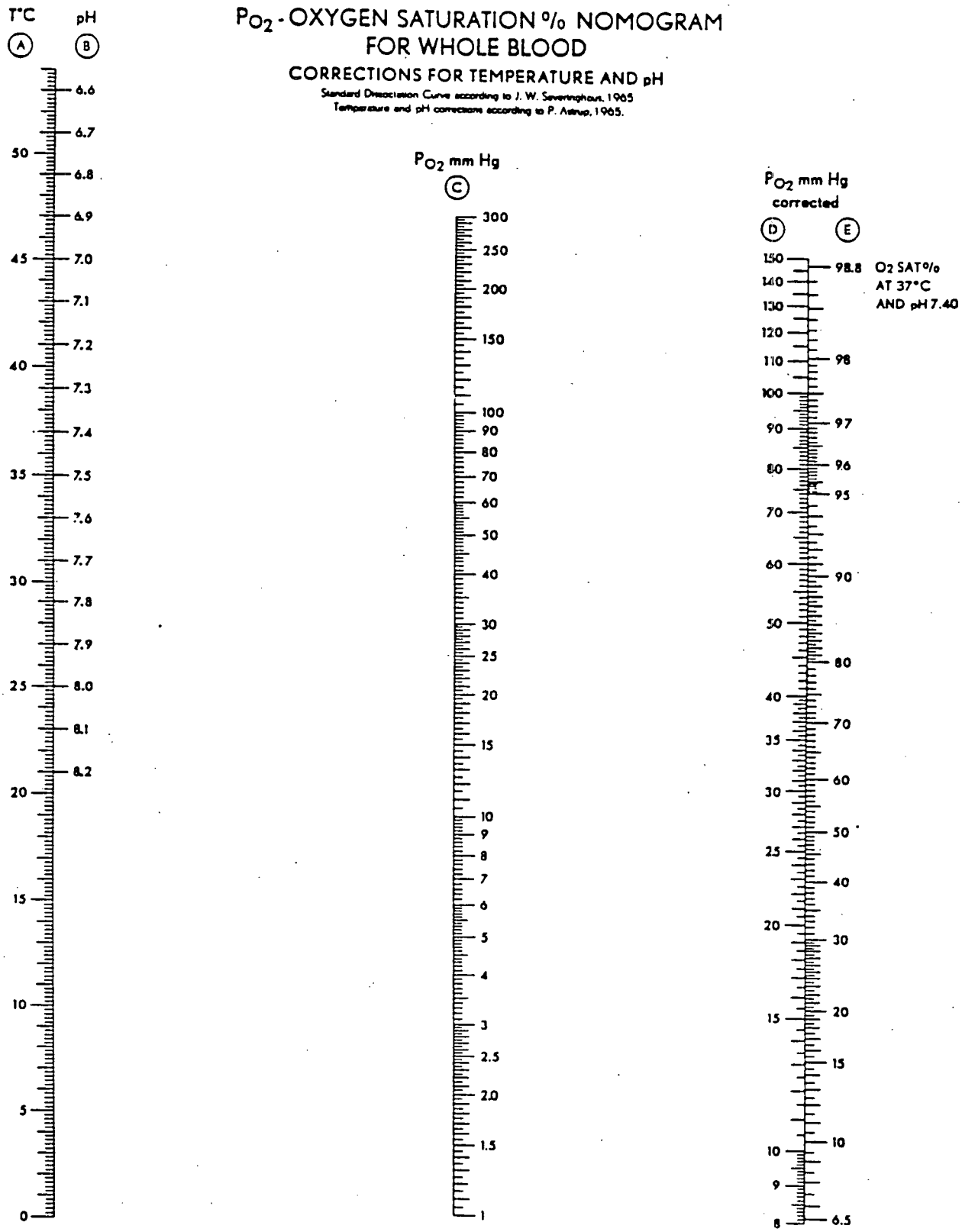
Hypoventilation: That hypoventilation plays a role in the genesis of arterial hypoxemia seems likely, but to what extent is uncertain. In the study of Dempsey et al., 1984, the individuals demonstrating the greatest degree of arterial hypoxemia exhibited the lowest hyperventilatory response to exercise. While these subjects did not retain CO_2 above resting levels, it may be considered in the light of significant metabolic acidosis, that normal levels of PCO_2 may be inappropriate.

Non-apneic arterial desaturation of 11% of more has been reported during sleep in patients with chronic obstructive pulmonary disease. Some authors (Littner et al., 1980) have described diminished ventilatory responses to hypoxia and hypercapnia during daytime wakefulness in these individuals compared to non-desaturating controls. In normal subjects quiet or non-REM sleep is associated with decreased ventilation, alterations in breathing pattern and mild hypoxia and hypercapnia; the hypoxic and hypercapnic ventilatory responses show some decrease. (Weil et al., 1984). In normal subjects SaO_2 is well maintained. Thus it can be seen that in some

circumstances desaturation is associated with diminished respiratory drives.

This review has focused on exercise ventilation and the possible mechanisms of arterial desaturation during heavy exercise. Of the four possible explainations for the decline in arterial desaturation, diffusion and inadequacy of ventilation either due to blunted respiratory drive or mechanical constraints are the are the most likely.

APPENDIX B



To read the corrected PO_2 (scale D) or SaO_2 (scale E) the measured temperature or pH is found on scale A or B and a straight line is drawn to the measured PO_2 on scale C.

APPENDIX C SUBJECT PHYSIOLOGIC DATA

SUBJECT	AGE (yrs)	HEIGHT (cms)	WEIGHT (kg)	$\dot{V}O_2MAX$ (ml/kg/min)	TREADMILL VELOCITY (m/sec)	HVR (1/%ΔSa_{O_2})
1	21	192.0	80.7	61.8	11.5	0.43
2	30	178.0	71.8	63.8	13.0	0.43
3	18	180.2	70.1	62.6	11.5	0.78
4	23	185.6	81.2	61.5	11.75	1.12
5	22	179.5	69.5	64.9	12.25	1.05
6	25	179.0	67.7	61.1	12.25	1.03
7	23	182.6	79.7	64.8	11.75	0.22
8	18	180.2	70.1	62.6	11.5	0.22
9	26	185.0	81.0	67.3	12.5	1.22
10	24	169.0	61.4	66.8	12.5	0.87
11	28	179.5	74.3	61.7	11.75	0.43
12	27	184.8	73.6	61.8	11.75	0.26

APPENDIX D PULMONARY FUNCTION TESTS

SUBJECT	FVC PRED. (1)	FVC MEASURED (1)	%	FEV 1 (1)	% FVC	PEAK FLOW (1/min)
1	6.34	6.05	95.4	4.94	86.1	442
2	5.17	5.13	99.2	3.79	73.8	333
3	5.89	6.47	109.8	5.74	88.7	655
4	5.91	5.72	96.8	4.16	72.7	391
5	5.51	6.07	110.2	3.47	57.1	487
6	5.38	4.53	84.2	3.71	81.9	482
7	5.64	5.12	90.8	3.65	71.2	316
8	5.64	4.84	85.8	3.83	79.1	401
9	5.41	6.18	114.2	4.39	71.0	532
10	4.76	4.29	90.1	3.37	78.6	473
11	5.26	5.37	1.02	4.31	80.2	492
12	5.71	5.30	92.8	4.56	86.0	500

APPENDIX E HYPOXIC VENTILATORY RESPONSE DATA

A and R^2 for the line $\dot{V}E = A(SaO2) + Vo$

SUBJECT	TEST ONE		TEST TWO		TEST THREE		HVR USED	COMMENTS
	A	R2	A	R2	A	R2		
1	0.41	0.80	0.45	0.82	-	-	0.43	mean of 1,2.
2	0.42	0.72	0.44	0.72	-	-	0.43	mean of 1,2.
3	0.78	0.70	-	-	-	-	0.78	
4	1.25	0.88	0.99	0.91	-	-	1.12	mean of 1,2.
5	1.05	0.70	-	-	-	-	1.05	
6	1.10	0.89	0.96	0.93	-	-	1.03	mean of 1,2.
7	0.15	0.29	0.08	0.25	0.28	0.40	0.22	mean of 1,3. poor CO2 control in 2.
8	0.22	0.63	0.07	0.12	0.21	0.81	0.22	mean of 1,3. two best fitting lines.
9	1.98	0.87	1.22	0.70	-	-	1.22	1 not used poor CO2 control
10	0.87	0.77	-	-	-	-	0.87	
11	0.43	0.77	0.14	0.45	-	-	0.43	1 used as best fit
12	0.18	0.49	-0.01	0.01	0.26	0.82	0.26	subject hyperventilated at start of 1,2.

$\dot{V}E$ is observed ventilation, $A = \Delta VE / 1\% \Delta SaO2$,
Vo is calculated ventilation when SaO2 = 0

APPENDIX F SUBJECT DATA

SUBJECT 1

TIME (min)	R	0:15	0:30	0:45	1:00	1:15	1:30	1:45	2:00	2:15	2:30	2:45	3:00	3:15	3:30	3:45	4:00	4:15	4:30	4:45	5:00
pH	7.434	7.442	7.848	7.463	7.463	7.436	7.417	7.404	7.391	7.380	7.371	7.365	7.355	7.345	7.337	7.341	7.320	7.310	7.300	7.285	7.285
PCO2 (torr)	36.5	35.3	37.7	37.7	36.0	36.1	39.3	34.1	36.1	35.4	36.9	34.6	37.2	36.7	36.4	32.9	32.6	37.3	30.3	31.7	30.5
PO2 (torr)	91	106	100	92	93	93	98	92	93	87	89	87	85	86	87	86	88	81	85	80	84
SaO2 (%)	97.4	98.3	98.2	97.6	97.7	97.5	97.7	97.3	97.2	96.5	96.7	96.4	96.0	96.0	96.0	96.1	96.1	94.8	95.4	94.4	95.0
$\dot{V}O2$(l/min)		1.33	2.78	3.95	4.52	4.20	4.58	4.32	4.65	4.28	4.62	4.64	4.42	4.82	4.77	4.62	4.87	4.78	4.78	4.70	4.86
$\dot{V}E$(l/min BTPS)		58.0	88.0	107.5	130.3	131.5	146.4	142.5	157.1	146.8	161.3	162.7	156.3	167.4	169.0	167.9	164.1	169.1	169.1	166.9	170.9

SUBJECT 2

TIME (min)	R	0:15	0:30	0:45	1:00	1:15	1:30	1:45	2:00	2:15	2:30	2:45	3:00	3:15	3:30	3:45	4:00	4:15	4:30	4:45	5:00
pH	7.442	7.465	7.451	7.431	7.408	7.380	7.353	7.353	7.337	7.319	7.279	7.260	7.242	7.230	7.213	7.201	7.183	7.165	7.146	7.137	7.122
PCO2 (torr)	36.5	34.1	38.7	35.8	39.4	40.4	40.6	40.9	40.0	36.4	39.4	39.9	40.0	38.5	39.3	38.6	38.5	38.4	38.4	38.5	38.1
PO2 (torr)	113	131	113	97	97	97	94	97	99	95	98	94	92	94	90	91	88	87	87	87	85
SaO2 (%)	98.6	99.2	98.6	97.8	97.6	97.4	97.0	97.2	97.3	98.6	96.6	96.0	95.5	95.7	94.9	94.9	94.1	93.7	93.3	93.1	92.4
$\dot{V}O2$(l/min)		1.44	1.84	3.42	3.67	3.81	3.88	3.95	3.94	3.96	3.96	4.10	4.11	4.17	4.10	4.25	4.23	4.18	4.14	4.21	3.90
$\dot{V}E$(l/min BTPS)		57.6	67.4	88.9	99.4	107.1	117.4	125.9	129.9	129.5	130.0	135.7	136.2	139.7	135.9	139.0	144.5	141.3	138.4	138.2	124.7

SUBJECT 3

TIME (min)	R	0:15	0:30	0:45	1:00	1:15	1:30	1:45	2:00	2:15	2:30	2:45	3:00	3:15	3:30	3:45	4:00	4:15	4:30	4:45	5:00
pH	7.440	7.444	7.458	7.453	7.449	7.429	7.423	7.405	7.400	7.388	7.382	7.375	7.367	7.368	7.351	7.353	7.351	7.346	7.334	7.331	7.328
PCO2 (torr)	34.2	36.6	37.1	38.4	37.8	37.8	34.2	40.2	36.4	36.2	34.0	35.9	33.0	34.3	34.6	32.9	32.3	32.6	35.6	35.1	32.2
PO2 (torr)	119	117	103	106	102	104	99	109	102	109	105	104	108	102	101	103	102	95	96	91	96
SaO2 (%)	98.8	98.8	98.3	98.4	98.2	98.2	97.9	98.3	97.9	98.2	98.0	97.9	98.1	97.8	97.6	97.7	97.6	97.1	97.0	96.5	97.0
$\dot{V}O2$(l/min)		1.48	2.39	3.47	3.70	3.86	3.59	3.78	3.81	3.88	3.69	3.85	4.02	3.86	4.00	4.12	4.03	3.95	4.28	4.09	4.15
$\dot{V}E$(l/min BTPS)		52.3	71.8	90.8	96.9	112.6	118.6	128.2	133.2	134.5	130.0	132.4	133.2	129.4	132.4	136.6	136.6	130.6	144.4	134.3	134.0

SUBJECT 4

TIME (min)	R	0:15	0:30	0:45	1:00	1:15	1:30	1:45	2:00	2:15	2:30	2:45	3:00	3:15	3:30	3:45	4:00	4:15	4:30	4:45	5:00
pH	7.440	7.442	7.442	7.431	7.417	7.396	7.384	7.368	7.335	7.338	7.322	7.311	7.295	7.282	7.272	7.266	7.256	7.244	7.230	7.221	7.207
PCO2 (torr)	38.4	38.1	39.2	37.0	37.9	40.2	37.4	37.9	38.1	38.0	40.9	39.6	37.3	36.8	39.4	38.7	37.3	36.3	37.2	37.4	35.7
PO2 (torr)	100	107	88	83	83	86	86	86	93	89	83	84	84	83	84	86	86	85	84	82	85
SaO2 (%)	98.0	98.4	97.1	96.5	96.4	96.5	96.4	96.3	96.8	96.3	95.3	95.2	95.1	94.7	94.8	95.0	94.9	94.5	94.1	93.0	94.0
$\dot{V}O2$(ml/min)		1.08	2.20	4.42	4.50	4.64	4.45	4.69	4.41	4.35	4.64	4.35	4.69	4.46	4.83	4.59	4.73	4.66	4.67	4.77	4.56
$\dot{V}E$(l/min BTPS)		39.3	57.2	89.4	96.2	107.8	112.4	124.6	124.8	117.8	123.1	121.1	129.7	121.7	136.8	133.9	140.7	150.5	132.8	140.3	140.4

SUBJECT 5

TIME (min)	R	0:15	0:30	0:45	1:00	1:15	1:30	1:45	2:00	2:15	2:30	2:45	3:00	3:15	3:30	3:45	4:00	4:15	4:30	4:45	5:00
pH	7.437	7.404	7.439	7.430	7.404	7.376	7.366	7.347	7.330	7.320	7.313	7.295	7.282	7.275	7.255	7.250	7.234	7.223	7.205	7.194	7.179
PCO2 (torr)	40.3	40.2	39.1	38.8	40.4	42.9	41.2	39.0	41.5	39.6	38.7	38.3	37.3	39.5	38.3	35.4	38.7	36.9	36.4	36.1	37.7
PO2 (torr)	105	107	105	96	92	93	95	92	89	88	87	86	86	83	82	82	80	80	81	81	79
SaO2 (%)	98.2	98.2	98.2	97.6	97.2	97.0	97.1	96.7	96.1	96.0	95.8	95.5	95.2	94.6	94.1	94.0	93.4	93,1	93.1	92.9	91.7
$\dot{V}O2$(1/min)		0.60	1.38	2.44	3.64	3.93	3.93	4.02	3.89	4.22	4.01	4.07	4.24	4.10	4.24	4.33	4.35	4.19	4.46	4.19	4.36
$\dot{V}E$(1/min BTPS)		22.8	55.2	76.3	96.3	107.4	114.1	123.6	124.1	134.7	129.5	134.6	139.8	131.6	137.9	139.0	140.2	137.8	145.7	139.6	144.7

SUBJECT 6

TIME (min)	R	0:15	0:30	0:45	1:00	1:15	1:30	1:45	2:00	2:15	2:30	2:45	3:00	3:15	3:30	3:45	4:00	4:15	4:30	4:45	5:00
pH	7.400	7.424	7.413	7.390	7.371	7.348	7.332	7.315	7.300	7.266	7.238	7.235	7.213	7.194	7.178	7.160	7.149	7.132	–	–	–
PCO2 (torr)	39.2	34.9	38.0	40.8	41.5	40.6	39.6	39.4	40.1	41.3	42.5	40.0	41.4	39.5	41.8	39.2	38.6	40.6	–	–	–
PO2 (torr)	106	122	101	94	95	95	92	93	90	87	84	88	83	83	81	84	81	81	–	–	–
SaO2 (%)	98.1	98.8	97.9	97.2	97.1	97.0	96.6	96.5	96.0	95.1	94.3	94.8	93.5	93.3	92.5	92.9	92.1	91.4	–	–	–
$\dot{V}O2$(1/min)		1.69	2.04	3.12	3.86	3.48	3.93	3.89	3.77	4.00	3.62	4.11	3.94	4.08	3.94	4.15	4.25	3.59	–	–	–
$\dot{V}E$(1/min BTPS)		59.6	76.0	86.5	103.7	106.1	121.3	125.5	122.8	128.6	120.6	131.7	130.5	133.3	127.2	130.1	137.5	120.0	–	–	–

SUBJECT 7

TIME (min)	R	0:15	0:30	0:45	1:00	1:15	1:30	1:45	2:00	2:15	2:30	2:45	3:00	3:15	3:30	3:45	4:00	4:15	4:30	4:45	5:00
pH	7.451	7.439	7.463	7.432	7.416	7.384	7.365	7.358	7.348	7.341	7.328	7.314	7.304	7.299	7.285	7.265	7.264	7.249	7.236	7.299	7.215
PCO2 (torr)	33.4	38.6	37.3	38.4	39.4	41.5	36.7	41.1	38.3	41.2	41.2	39.7	36.6	39.5	41.5	38.5	39.9	40.3	41.3	40.9	41.1
PO2 (torr)	100	112	107	96	86	86	85	84	89	84	87	80	78	79	85	86	77	76	75	79	75
SaO2 (%)	91.8	98.5	98.5	97.7	96.7	96.4	96.2	95.8	96.3	95.6	95.9	94.7	94.1	94.2	95.0	95.1	93.1	92.6	92.1	93.1	91.5
$\dot{V}O_2$(l/min)		2.84	3.14	4.41	4.98	4.79	4.88	5.00	5.20	4.90	5.07	5.22	5.07	4.96	5.19	4.95	5.23	5.10	5.15	5.15	4.96
$\dot{V}E$(l/min BTPS)		92.6	103.3	111.8	128.5	127.8	129.3	132.3	143.9	137.5	143.0	148.1	143.6	143.0	150.0	142.6	150.1	146.4	150.7	150.3	145.1

SUBJECT 8

TIME (min)	R	0:15	0:30	0:45	1:00	1:15	1:30	1:45	2:00	2:15	2:30	2:45	3:00	3:15	3:30	3:45	4:00	4:15	4:30	4:45	5:00
pH	7.460	7.431	7.424	7.411	7.397	7.377	7.362	7.350	7.322	7.318	7.300	7.289	7.277	7.263	7.247	7.236	7.218	7.215	7.203	7.196	7.182
PCO2 (torr)	32.9	38.8	39.7	40.3	39.8	35.7	38.3	38.2	37.3	36.4	38.6	37.8	39.6	36.3	37.8	36.6	37.6	34.2	35.5	35.0	36.0
PO2 (torr)	109	78	77	82	79	80	83	82	79	82	79	76	78	78	73	73	73	74	74	75	74
SaO2 (%)	98.6	95.8	95.5	96.1	95.5	95.5	95.8	95.4	94.8	95.1	94.2	93.5	93.8	93.4	91.9	91.6	91.1	91.4	91.2	91.2	90.8
$\dot{V}O_2$(l/min)		1.78	3.11	3.72	3.82	3.79	3.92	3.83	3.82	3.92	4.05	3.92	4.09	3.94	3.89	4.22	4.23	4.22	4.11	4.07	3.98
$\dot{V}E$(l/min BTPS)		47.3	69.6	85.3	98.9	107.7	118.7	123.7	124.2	127.7	134.6	133.0	136.6	138.2	133.7	137.6	141.4	144.2	140.8	145.8	137.2

SUBJECT 9

TIME (min)	R	0:15	0:30	0:45	1:00	1:15	1:30	1:45	2:00	2:15	2:30	2:45	3:00	3:15	3:30	3:45	4:00	4:15	4:30	4:45	5:00
pH	7.431	7.473	7.472	7.469	7.437	7.422	7.392	7.384	7.368	7.355	7.335	7.327	7.312	7.298	7.284	7.277	7.259	7.248	7.233	7.219	7.208
PCO2 (torr)	38.3	31.4	34.4	35.4	36.2	36.0	36.6	36.6	36.6	36.4	36.7	36.8	36.7	36.6	35.9	36.9	36.9	34.7	36.1	35.9	35.6
PO2 (torr)	107	123	122	103	91	91	84	87	83	82	78	78	77	76	73	72	72	73	70	70	71
SaO2 (%)	98.3	99.9	99.0	98.3	97.4	97.3	96.3	96.5	95.9	95.6	94.7	94.4	94.1	93.7	92.7	92.3	91.7	91.9	90.6	90.2	90.1
$\dot{V}O2$(l/min)		1.09	2.30	4.15	4.94	4.74	4.67	5.10	5.07	5.13	5.18	5.24	5.43	4.32	5.44	5.52	5.37	5,45	5.58	5.43	5.59
VE(l/min BDPS)		46.1	87.1	130.6	157.1	166.9	167.2	181.5	185.6	183.2	183.1	185.6	188.1	181.9	184.8	187.0	179.3	182.5	184.8	179.2	184.7

SUBJECT 10

TIME (min)	R	0:15	0:30	0:45	1:00	1:15	1:30	1:45	2:00	2:15	2:30	2:45	3:00	3:15	3:30	3:45	4:00	4:15	4:30	4:45	5:00
pH	7.434	7.475	7.478	7.430	7.417	7.405	7.373	7.360	7.331	7.313	7.286	7.280	7.273	7.254	7.236	7.226	7.209	7.198	7.187	7.190	7.161
PCO2 (torr)	27.4	30.3	32.7	31.4	35.2	35.2	36.8	35.8	36.2	35.8	33.6	37.4	34.1	33.8	35.4	34.5	35.5	34.6	35.4	33.0	35.7
PO2 (torr)	125	117	103	91	89	91	89	87	86	86	83	81	84	84	78	81	77	77	76	75	75
SaO2 (%)	99.0	98.9	98.4	97.4	97.1	97.2	96.7	96.3	95.9	95.7	94.9	94.5	94.8	94.7	93.1	93.6	92.1	92.0	91.5	91.4	90.6
$\dot{V}O2$(l/min)		1.61	2.11	3.57	3.88	3.65	3.85	3.87	4.13	4.07	4.17	4.30	4.21	4.15	4.36	4.13	4.35	4.40	4.35	4.40	4.14
VE(l/min BTPS)		66.8	90.2	114.5	128.0	129.8	134.4	139.2	148.3	145.9	151.2	155.7	151.5	148.2	154.5	147.4	151.2	156.2	151.2	152.5	141.4

SUBJECT 11

TIME (min)	R	0:15	0:30	0:45	1:00	1:15	1:30	1:45	2:00	2:15	2:30	2:45	3:00	3:15	3:30	3:45	4:00	4:15	4:30	4:45	5:00
pH	7.443	7.470	7.480	7.455	7.439	7.436	7.395	7.379	7.357	7.340	7.331	7.317	7.298	7.285	7.268	7.260	7.244	7.242	7.123	7.213	7.207
PCO2 (torr)	44.1	40.3	43.4	36.3	35.8	38.7	39.2	39.2	42.6	41.3	39.8	40.8	41.2	41.3	42.3	41.0	40.8	40.4	40.6	38.9	41.8
PO2 (torr)	101	126	106	98	88	83	89	77	75	74	73	73	70	70	69	70	70	71	69	68	66
SaO2 (%)	98.0	99.1	98.4	98.0	97.1	96.6	96.9	95.0	94.3	93.8	93.4	93.2	92.0	91.6	90.9	91.0	90.5	91.0	89.7	89.1	88.1
$\dot{V}O2$(l/min)		2.07	2.65	4.09	4.22	3.98	4.19	4.45	4.42	4.43	4.62	4.41	4.52	4.65	4.58	4.75	4.67	4.64	4.68	4.60	4.80
$\dot{V}E$(l/min BTPS)		89.5	105.7	143.9	143.9	136.6	141.6	150.9	151.2	152.6	156.4	151.0	151.9	151.7	150.9	155.2	154.2	152.2	153.6	153.1	159.4

SUBJECT 12

TIME (min)	R	0:15	0:30	0:45	1:00	1:15	1:30	1:45	2:00	2:15	2:30	2:45	3:00	3:15	3:30	3:45	4:00	4:15	4:30	4:45	5:00
pH	7.440	7.424	7.436	7.406	7.394	7.375	7.365	7.342	7.336	7.336	7.327	7.314	7.307	7.289	7.281	7.272	7.261	7.260	7.241	7.231	7.228
PCO2 (torr)	34.4	32.0	36.5	37.4	37.9	35.7	39.3	40.0	38.4	37.7	36.5	37.5	37.7	37.2	37.8	37.0	37.2	36.1	36.1	35.4	35.7
PO2 (torr)	113	98	94	75	76	76	76	76	75	74	75	71	71	71	67	69	68	68	70	68	71
SaO2 (%)	98.6	97.9	97.6	95.0	95.0	94.9	94.7	94.2	94.0	93.8	94.0	93.7	92.5	92.0	90.7	91.3	90.6	90.7	90.7	90.0	90.9
$\dot{V}O2$(l/min)		1.31	2.08	4.61	3.93	4.13	4.13	4.37	4.38	4.44	4.07	4.38	4.30	4.26	4.44	4.45	4.63	4.22	4.58	4.56	4.62
$\dot{V}E$(l/min BTPS)		62.3	70.0	103.8	102.7	109.5	108.7	116.0	125.8	138.9	131.0	133.6	129.7	125.9	129.5	128.9	136.0	129.6	136.2	140.3	145.4

APPENDIX G

EQUIPMENT AND SUPPLIES:

Equipment:

1. Cardiac monitor
2. Beckman Metabolic Measurement cart
3. Hewlett-Packard data aquisition system
4. spirometer
5. CO2 sensor
6. O2 sensor
7. breathing bag and circuit
8. nitrogen gas and two way Rudolph valve
9. carbon dioxide gas
10. blood gas analyzer
11. treadmill
12. clock
13. pneumotach
14. ear oximeter

Supplies:

1. Arterial cannulas.....20
2. plastic syringes.....100
3. # 22 gauge needles.....100
4. # 18 gauge needles.....20
5. 20 cc syringes.....20
6. 5 cc syringes.....20
7. #20 butterfly i.v. 20
8. heparin locks.....20
9. OP-site.....20
10. compression tape.....1 roll
11. heparin 1000 u/ml 10ml.....5 bottles
12. normal saline 500 ml.....16 bags
13. bandages
14. alcohol swabs
15. 2x2 gauze

Personnel:

Day one:
1- pulmonary function tests
2- treadmill run and Beckman

Day two: Exercise test
1-timer 1-laboratory assistant
1-sampler

Day three:
1-recorder
1-gas mixture

APPENDIX H EXERCISE VENTILATION STUDY

The purpose of this study is to relate the changes in arterial oxygen concentration and breathing during heavy physical work.

The subjects are recruited on a volunteer basis and are normal healthy males who are highly trained. On the first testing session you will have measures of your lung functions and maximum voluntary ventilation. This entails breathing through a mouthpiece so that your volume of expiration and flow rate can be measured. These procedures are not associated with any significant risk. Following these determinations you will be asked to breathe through another apparatus. During this measure the concentration of oxygen in the inspired gas will be gradually be decreased and the change in your breathing in response to this will be measured. This procedure will be done under medical supervision and your heart will be monitored through out. Extremely rarely irregularities in heart rhythm have been reported with this procedure. Other complications have not been reported.

On the next testing session, you will have your maximal oxygen uptake according to established study protocol on a treadmill. The work load on the treadmill will be increased, in stages until you are unable to continue, while the gas concentrations are determined in your expired gas as you breathe through a mouthpiece. The risks of this procedure are minimal; some minor discomfort in the jaw muscles and some increased awareness of your breathing may be noticed.

Once your maximal oxygen uptake is determined,you will be brought back on another day and will perform a five minute run at 100% of your $\dot{V}O_2$ max. During this run you will again breathe through the mouth piece so that your rate of ventilation can be measured. Also at this time you will have an indwelling canula in your radial artery. This procedure involves some minor discomfort similar to that of having a conventional blood sample taken. The risks of this procedure will be minimized by using trained physician with special expertise in this procedure. These risks include a small chance of infection or increased bleeding at the site of the puncture. In extremely rare instances an aneurism or dilation at the site of the catheter insertion could occur. Spasm of the artery causing impaired blood supply to the hand could also occur rarely and you will be checked to insure adequate alternate blood supply prior to insertion of the cannula.

The benefits of the study include the opportunity to participate in physiologic research, and the opportunity to have a VO_2 max determination. IF YOU HAVE ANY QUESTIONS ABOUT THE STUDY PROCEDURES WE WILL BE HAPPY TO ANSWER THEM NOW OR AT ANY TIME.

I have read and understand the above and agree to participate in the study. I understand that I have the right to withdraw at any time, without question.

DATE:_____ SIGNATURE:_____

WITNESS: _____