Peripheral Chemoresponsiveness and Exercise Induced Arterial Hypoxemia
in Highly Trained Endurance Athletes.

by

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ABSTRACT

To determine whether highly trained endurance athletes (HT) who develop exercise induced arterial hypoxemia (EIH) also demonstrate reduced peripheral chemoresponsiveness (PC) during exercise, twelve (N=12) HT male cyclists were selected for study. Basic pulmonary function data (FEV_1 = 4.69 ± 0.66 L, FVC = 6.12 ± 0.82 L, $FEV_{1.0}$/FVC = 0.77 ± 0.08, FEF_{max} = 10.52 ± 1.57 $L \cdot sec^{-1}$, and MVV = 194 ± 21 $L \cdot min^{-1}$) were obtained on all subjects. Subjects exercised on a cycle ergometer to exhaustion to determine their maximal aerobic capacity ($\dot{V}_{O2max}$ = 5.08 ± 0.32 $L \cdot min^{-1}$, 66.6 ± 4.7 $mL \cdot min^{-1} \cdot kg^{-1}$), and ventilatory threshold ($\dot{V}_{O2TH}$ = 3.29 ± 0.12 $L \cdot min^{-1}$, 44.3 ± 4.2 $mL \cdot min^{-1} \cdot kg^{-1}$). Oxygen saturation of arterial hemoglobin (S_aO_{2max}) was monitored with an ear oximeter (Hewlett-Packard, 47201A), to determine whether subjects exhibited EIH ($S_aO_{2max} \leq 91\%$) during the maximal cycle ergometer test. Subjects with $S_aO_{2max} \geq 93\%$ were placed in the normal saturation group (NOS, S_aO_{2max} = 93.4 ± 0.4 %) while subjects whose $S_aO_{2max} \leq 91\%$ were placed in the low saturation group (LOS, S_aO_{2max} = 89.9 ± 0.9 %). Ventilatory responses to hypercapnic (13% CO_2, 21% O_2, 66% N_2) and hyperoxic (100% O_2) gas mixtures were determined at rest, and during exercise on a cycle ergometer at approximately 25% $\dot{V}_{O2max}$, 50% $\dot{V}_{O2max}$, $\dot{V}_{O2TH}$. Hypercapnic peripheral chemoresponsiveness was lower in LOS subjects than NOS subjects and increased in both groups from rest to 50 % $\dot{V}_{O2max}$. Hyperoxic peripheral chemoresponsiveness was not different in LOS and NOS subjects and did not change with exercise. Pre-stimulus S_aO_2 fell significantly during exercise in all subjects with LOS having lower S_aO_2 than NOS at $\dot{V}_{O2TH}$ during the hypercapnic chemoresponse tests only. No evidence for a relationship between pre-stimulus S_aO_2 and either hypercapnic or hyperoxic peripheral chemoresponsiveness was found. The results

of this study provide information which may help explain variations in the ventilatory response to exercise in athletes. Additionally, data from this study suggest a role of altered ventilatory control in highly trained endurance athletes who do and do not demonstrate exercise induced arterial hypoxemia.

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LIST OF ABBREVIATIONS AND SYMBOLS

$(A\text{-}a)DO_2$	Alveolar-arterial oxygen difference.
$[H^+]_a$	Arterial hydrogen ion concentration.
EIH	Exercise induced arterial hypoxemia.
$F_{(x,y)group}$	Omnibus F ratio for RMANOVA group main effect with x numerator degrees of freedom, and y denominator degrees of freedom.
$F_{(x,y)trials}$	Omnibus F ratio for RMANOVA trials main effect with x numerator degrees of freedom, and y denominator degrees of freedom.
$F_{(x,y)int}$	Omnibus F ratio for RMANOVA trials x group interaction with x numerator degrees of freedom, and y denominator degrees of freedom.
$F_{(1,y)lin}$	Omnibus F ratio for linear polynomial contrast with 1 numerator degree of freedom, and y denominator degrees of freedom.
$F_{(1,y)lin\ int}$	Omnibus F ratio for group interaction of linear polynomial contrast with 1 numerator degree of freedom, and y denominator degrees of freedom.
$F_{(1,y)quad}$	Omnibus F ratio for quadratic polynomial contrast with 1 numerator degree of freedom, and y denominator degrees of freedom.
$F_{(1,y)quad\ int}$	Omnibus F ratio for group interaction of quadratic polynomial contrast with 1 numerator degree of freedom, and y denominator degrees of freedom.
f_R	Respiratory frequency.
FVC	Forced vital capacity.

FEV_1	Forced expired volume in first second.
FEF_{max}	Maximal expiratory flow rate.
GDiC	Line of general direction of change.
HT	Highly trained endurance athletes.
$[K^+]a$	Arterial potassium ion concentration.
LPO	Low power output, 50% of maximal aerobic power.
MPO	Moderate power output, aerobic power at ventilatory threshold.
MVV	Maximal voluntary ventilation.
P_ACO_2	Alveolar partial pressure of carbon dioxide.
P_AO_2	Alveolar partial pressure of oxygen.
P_aCO_2	Arterial partial pressure of carbon dioxide.
P_aO_2	Arterial partial pressure of oxygen.
PC	Peripheral chemoresponsiveness.
PCO_2	Partial pressure of carbon dioxide.
$P_{ET}CO_2$	End-tidal partial pressure of carbon dioxide.
$P_{ET}O_2$	End-tidal partial pressure of oxygen.
pH	Negative logarithm of hydrogen ion concentration.
pH_a	Negative logarithm of hydrogen ion concentration in arterial blood.

P_{O_2}	Partial pressure of oxygen.
$\dot{Q}_C$	Perfusion.
RMANOVA	Repeated-measures analysis of variance.
S_aO_2	Oxygen saturation of arterial hemoglobin.
S_aO_{2max}	Minimal oxygen saturation of arterial hemoglobin during maximal cycle ergometer test.
$\dot{V}_A$	Alveolar ventilation.
$\dot{V}_A$:$\dot{Q}_C$	Ventilation-perfusion ratio.
$\dot{V}_{CO_2}$	Rate of carbon dioxide elimination.
V_E	Volume of air expired.
$\dot{V}_E$	Expired ventilation, or volume of air expired per minute.
$\dot{V}_E/\dot{V}_{CO_2}$	Ventilatory equivalent for carbon dioxide elimination.
$\dot{V}_E/\dot{V}_{O_2}$	Ventilatory equivalent for oxygen consumption.
V_I	Volume of air inspired.
$\dot{V}_I$	Inspired ventilation, or volume of air inspired per minute.
VLPO	Very low power output, 25% of maximal aerobic power.
$\dot{V}_{O_2}$	Rate of oxygen uptake.
$\dot{V}_{O_2max}$	Maximal rate of oxygen uptake.

$\dot{V}_{O2TH}$ Rate of oxygen consumption at the ventilatory threshold.

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INTRODUCTION

A number of authors (11, 20, 39-41, 43) have reported a decrease in partial pressure of oxygen in arterial blood and/or desaturation of hemoglobin during intense exercise in highly trained endurance athletes. This phenomenon has been called exercise induced arterial hypoxemia and its incidence has been reported to be between 40 (42) and 52 percent (39) in highly trained male endurance athletes. The occurrence of exercise induced arterial hypoxemia in highly trained athletes is reproducible with at least one group (39) finding a test/retest correlation of 0.95, $p<.05$.

The most likely causes of exercise induced arterial hypoxemia are: alveolar ventilation ($\dot{V}_A$) to perfusion ($\dot{Q}_C$) heterogeneity ($\dot{V}_A:\dot{Q}_C$), veno-arterial shunt, diffusion disequilibrium, and the absence of adequate compensatory hyperventilation (10, 20, 49). In normal individuals and those highly trained athletes who do not demonstrate exercise induced arterial hypoxemia , $\dot{V}_A:\dot{Q}_C$ heterogeneity and veno-arterial shunt account for the widening of the alveolar-arterial O_2 difference from less than 5 torr at rest to approximately 30 torr during heavy exercise(9). Athletes with high cardiac outputs ($\approx$ 33 $L \cdot min^{-1}$) and maximal pulmonary blood volumes ($\approx$ 1.6 L) are likely to have very short red blood cell pulmonary transit times (10, 19). In addition, the absence of adequate exercise hyperpnea would result in a lowering of alveolar PO_2 on a breath by breath basis. The rate of equilibration of O_2 would then decrease on a breath by breath basis due to a lowering of the O_2 driving pressure across the gas exchange barrier. This results in a subsequent fall in arterial PO_2 accompanied by the maintenance of a constant alveolar-arterial O_2 difference. Another mechanism which may be related to the high cardiac outputs and maximal pulmonary blood volumes seen in the highly trained athletes who exhibit exercise induced arterial hypoxemia, is pulmonary edema. There may be a

decrease in diffusion of O_2 across the alveolar membrane which is caused by an increase in the diffusion distance associated with the extravascular lung water accompanying pulmonary edema (33, 44, 45, 52, 53). Thus, shortened red blood cell pulmonary transit time and pulmonary edema may result in a significant diffusion disequilibrium at the end of the pulmonary capillary. These mechanisms, together with ventilation-perfusion heterogeneity and relative hypoventilation, are likely to explain the additional widening of the alveolar-arterial O_2 difference to approximately 45 torr in highly trained athletes who develop exercise induced arterial hypoxemia (9).

Conflicting data have been reported regarding the level of compensatory hyperventilation associated with heavy exercise and the influence it may have on exercise induced arterial hypoxemia. Relative hypoventilation has been associated with hypoxemia during exercise at 75 - 90 % $\dot{V}_{O_2max}$ (11) while another group (20) did not find evidence for such a hypoventilation accompanying a similar level of exercise induced arterial hypoxemia during exercise at essentially $\dot{V}_{O_2max}$. The difference between methodologies in these studies could explain the disagreement in their results. At maximal exercise intensities the accumulated ventilatory drive associated with the demand for CO_2 elimination may become so strong that hypoventilation is not present under these circumstances when it may have been present at lower exercise intensities. In a subsequent study (19), a relationship was found between P_aO_2 and ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$) supporting the hypothesis that hypoventilation plays a role in exercise induced arterial hypoxemia.

The ultimate goal of the respiratory system is the maintenance of blood homeostasis with respect to P_aO_2, partial pressure of carbon dioxide (CO_2) in arterial blood (P_aCO_2), and hydrogen ion concentration in arterial blood ($[H^+]_a$). Studies

involving carotid body resection in human subjects (17, 18, 50, 56) have shown that the peripheral chemoreceptors play an important role in the control of the acute ventilatory response to hypoxia and hypercapnia. The responsiveness of the peripheral chemoreceptors or the integration of their feedback in the brain stem are responsible, in part, for the inter-individual differences in the ventilatory response to changes in P_aO_2, P_aCO_2, $[H^+]_a$, exercise (9), and possibly potassium (37). Studies investigating the ventilatory responses of trained and untrained individuals have reported conflicting results. One study reported the chemoresponsiveness of individuals to increase with training (25), while other authors have reported that highly trained athletes have similar (29) and lower (5, 54) chemoresponsiveness than untrained individuals. Studies comparing the chemoresponsiveness of humans and animals at rest and exercise have also reported conflicting results. One group (31) found a correlation between $\dot{V}_E$ and hypercapnic peripheral chemoresponse in man while another (1) did not find such a relationship in the cat. It is clear that chemoresponsiveness is highly variable between individuals and it is this variability that could explain some of the differences in the results of these studies. However, like the incidence of exercise induced arterial hypoxemia, chemoresponsiveness at rest and mild exercise has been relatively reproducible, with reported mean coefficients of variation ($\bar{V}$) ranging from $23 \pm 15\%$ (46) to 25 ± 6 % (32).

It is interesting to note that reductions in P_aO_2 and/or S_aO_2 have been found at exercise intensities below maximum and near the ventilatory threshold (11, 19). A relative hypoventilation, possibly mediated through reduced peripheral chemoresponsiveness could explain the development of exercise induced arterial hypoxemia at these workloads in some athletes. For this reason this study was designed to

investigate the peripheral chemoresponsiveness of highly trained athletes, who do and do not develop exercise induced arterial hypoxemia , during very light, light, and moderate exercise. The relationship between peripheral chemoresponsiveness and the development of exercise induced arterial hypoxemia during exercise was also examined. Our general research questions were:

1. Is there a significant difference in peripheral chemoresponsiveness between rest, very light, light, and moderate exercise in subjects who do and do not demonstrate exercise induced arterial hypoxemia ?
2. Is there a significant difference in the pattern of change of peripheral chemoresponsiveness, across exercise levels, between subjects who do and do not demonstrate exercise induced arterial hypoxemia ?
3. Is there a significant decrease in S_aO_2 from rest to very light, light, and moderate exercise in subjects who do and do not demonstrate exercise induced arterial hypoxemia ?
4. Is there a significant difference in the pattern of change of S_aO_2 , across exercise levels, between subjects who do and do not demonstrate exercise induced arterial hypoxemia ?
5. Is there a relationship between peripheral chemoresponsiveness and S_aO_2 measured at each exercise level in subjects who do and do not demonstrate exercise induced arterial hypoxemia .

Our hypotheses with regards to the research questions we were interested in were:

1. There is a reduction in peripheral chemoresponsiveness from rest to very light, light, and moderate exercise in subjects who do and do not demonstrate exercise induced arterial hypoxemia .

2. Subjects who demonstrate exercise induced arterial hypoxemia have lower peripheral chemoresponsiveness than subjects who do not demonstrate exercise induced arterial hypoxemia at all exercise levels.
3. There is a reduction in S_aO_2 from rest to very light, light, and moderate exercise in subjects who do and do not demonstrate exercise induced arterial hypoxemia .
4. Subjects who do not demonstrate exercise induced arterial hypoxemia will demonstrate an initial fall in S_aO_2 from rest to light and perhaps very light exercise but will not demonstrate a further fall in S_aO_2 at moderate exercise intensities. Subjects who do demonstrate exercise induced arterial hypoxemia will demonstrate a fall in S_aO_2 from rest to light, very light, and moderate exercise.
6. Regression analysis of S_aO_2 and peripheral chemoresponsiveness, measured at each exercise level in subjects who do and do not demonstrate exercise induced arterial hypoxemia , will have a positive correlation coefficient.

METHODS

SUBJECTS

Highly trained male cyclists were recruited through personal contact or through advertisements in the Cycling British Columbia monthly newsletter and gave informed consent prior to participation in any experiments. Prior to participation in the study, subjects answered questions that increased the likelihood that they would satisfy the inclusion criteria which were: 1) normal pulmonary function with no history of pulmonary disease and 2) $\dot{V}_{O_2max} \geq 5.0$ L·min^{-1} or 60.0 mL·min^{-1}·kg^{-1}.

RESTING PULMONARY FUNCTION TESTS

Pulmonary function was tested using a MedGraphics CPX/D system equipped with pulmonary function software. The CPX/D system was calibrated prior to each testing session by withdrawing and injecting a known volume (5 x 3.00 Liters) through the pneumotach (MedGraphics, disposable) at various flow rates.

Each subject performed a minimum of three flow:volume maneuvers in order to obtain a reproducible measurement (according to ATS standards) of forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), ratio of forced expiratory volume in one second to forced vital capacity (FEV_1/FVC) and maximal forced expiratory flow rate (FEF_{max}). In addition, subjects performed at least two maximal voluntary ventilation (MVV) maneuvers. Data obtained were compared to normative values generated by the MGC CPX/D software. If subject values for FVC, $FEV_{1.0}$, $FEV_{1.0}$/FVC, FEF_{max} or MVV fell below the normal range, then subjects were excluded from further study.

MAXIMAL CYCLE ERGOMETER TEST

Subjects completed a progressive intensity test to volitional fatigue on an electronically braked cycle ergometer (Mijnhardt, KEM-3). Subjects used their own pedals and cycling shoes on the cycle ergometer and adjustments were made to the saddle and handlebars to approximate their normal riding position. Prior to testing subjects warmed-up either by riding at a slow pace to the testing facility on their bicycle or by pedaling on the cycle ergometer until they felt ready to begin. During the progressive intensity test subjects pedaled at their preferred pedal frequency (between 30 and 100 revolutions·min^{-1}) at a steadily increasing work rate (30 Watts·min^{-1} ramp) from zero load until they discontinued the test, or their pedaling frequency fell below 30 revolutions·min^{-1}. During the test subjects breathed through a two-way, non-rebreathing valve (Hans-Rudolph, #2700B). The inspired gas volume (Vacumetrics, #17150 air flow meter), and expired gas O_2 (Applied Electrochemistry, Oxygen Sensor N-22M and Oxygen Analyzer S-3A/I) and CO_2 (Beckman, LB-2) contents were monitored and recorded by a personal computer for analysis (Rayfield system). Every fifteen seconds the computer system calculated and displayed the expired minute ventilation ($\dot{V}_E$) and the rates of oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide elimination ($\dot{V}_{CO_2}$). After the test was completed the $\dot{V}_{O_2}$ at the ventilatory threshold ($\dot{V}_{O_2TH}$) was determined according to a previously documented computer technique (6). In summary, for each subject, a third order polynomial curve was fitted to a plot of $\dot{V}_{CO_2}$ versus $\dot{V}_{O_2}$ using least-squares regression. In addition, a straight line indicating the general direction of change (GDiC) was fitted between the endpoints of the polynomial curve fit. Beginning at the lowest measured $\dot{V}_{O_2}$ the computer calculated the distance between the predicted value of the polynomial curve fit and the GDiC perpendicular to the GDiC. This

calculation was repeated at 10 mL $\dot{V}_{O_2}$ intervals with the largest difference (Dmax) producing the $\dot{V}_{O_2TH}$ for that subject. Work rates at approximately 25% of $\dot{V}_{O_2max}$, 50% of $\dot{V}_{O_2max}$ and $\dot{V}_{O_2TH}$ were determined from linear least squares regression analysis of $\dot{V}_{O_2}$ and power output. Percent saturation of hemoglobin in arterial blood (S_aO_2) was measured with an ear oximeter (Hewlett-Packard, 47201A) and recorded on another personal computer (1 Hz) for later analysis. Prior to placement of the ear sensor a topical vasodilator cream (Finalgon®, Boehringer/Ingelheim) was applied to the pinna of the ear to enhance perfusion. The S_aO_2 data obtained during the progressive intensity test was smoothed as a 30 second moving mean with the lowest value chosen as S_aO_{2max}. The level of S_aO_{2max} chosen for inclusion into the LOS group ($S_aO_{2max} \leq 91.0$ %) was based on the definition of exercise induced arterial hypoxemia reported previously (39). The level of S_aO_{2max} chosen for inclusion into the NOS group ($S_aO_{2max} \geq 93.0$ %) was chosen to differentiate the NOS subjects as much as possible from subjects in the LOS group. Subjects satisfying these criteria who could not be assigned to either the exercise induced arterial hypoxemia group (LOS) or the normal group (NOS) based upon results in the maximal cycle ergometer test were excluded from further study.

CHEMORESPONSE TESTS

Ventilatory responses to hypercapnia and hyperoxia were determined at rest and while the subjects exercised at approximately 25% of $\dot{V}_{O_2max}$ (very low power output, VLPO), 50% of $\dot{V}_{O_2max}$ (low power output, LPO) and $\dot{V}_{O_2TH}$ (moderate power output, MPO). The chemoresponse trials at rest and each exercise intensity were performed on different days at least 24 hours after training. Subjects reported to the lab at least two hours after eating or drinking caffeine. During the resting determinations, subjects

remained in a supine position on a cot. Prior to exercise determinations, subjects adjusted the cycle ergometer then warmed-up for 5-10 minutes at approximately 50% of their exercise work rate. During all determinations subjects listened to music from a radio or with earphones.

Apparatus

The same apparatus was used for the hypercapnic and hyperoxic chemoresponse tests. The subjects breathed through the pneumotach of the CPX/D system which was connected to a differential pressure transducer (MedGraphics, disposable; Validyne, DP250). The flow measurement system of the CPX/D was calibrated by withdrawing and injecting a known volume through the pneumotach at various flow rates. A sample of inspired and expired gas was continuously taken from the CPX/D pneumotach and was analyzed by the fast response CPX/D gas analyzers (Medical Graphics Corporation, O_2 - zirconia fuel cell, CO_2 - infrared absorption). The CPX/D gas analyzers were calibrated with test gases of known composition. This enabled the approximate monitoring of $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, and $\dot{V}_E$ on a breath-by-breath basis as well as an accurate record of end-tidal O_2 and CO_2 pressures ($P_{ET}O_2$ and $P_{ET}CO_2$) during the steady-state period preceding the chemoresponse tests. The $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, and $\dot{V}_E$ data obtained and displayed in real time on the CPX/D system were not accurate due to the variations in inspired and expired gas composition that accompanied the chemoresponse tests. This was primarily due to the effect of gas density on flow measurements but was also a factor of the inability of the CPX/D software to accommodate the input from the gas analyzers during and after chemoresponse trials (see Figures 1a and 5a). The raw analyzer outputs of the CPX/D analyzers were channeled through an A/D board to a personal computer where the

appropriate offset and scale factors were applied to the raw signals enabling the real time display of PO_2 and PCO_2 during the chemoresponse tests. The CPX/D flow signal was used to confirm the timing of the flow signal on the inspiratory side of the breathing circuit (see below). The distal end of the CPX/D pneumotach was connected to a two-way non-rebreathing valve (Hans-Rudolph, #2700B). The inspiratory port of the non-rebreathing valve was connected to the outlet of a 4-way t-type valve (Hans-Rudolph,). Three of the inlets of the 4-way valve were connected to three ports of a bag-in-box system in the following manner. One of the inlets of the 4-way valve was connected to a port that was continuous with the interior of the airtight plexiglass box (volume $\approx$ 250 liters). The second inlet was connected to a port that was continuous with one 60 liter Douglas bag inside the box that was partially filled with the hyperoxic gas mixture. The third inlet was connected to a port that was continuous with a second 60 liter Douglas bag inside the box that was partially filled with the hypercapnic gas mixture. The fourth port of the bag-in-box system was connected to the pneumotach and differential pressure transducer of a Medical Graphics MGC/2001 metabolic cart (Hans-Rudolph, #3800; Validyne, DP250). The flow measurement system of the MGC/2001 was calibrated by repeatedly injecting a known volume through the pneumotach at various flow rates. The flow signal of the MGC/2001 system was channeled through the A/D board and into the personal computer where the appropriate offset and scale factors were applied, the signal was integrated and the resulting inspired volume (V_I) signal was displayed in real time. Using this system, V_I was accurately determined by measuring inspired air of constant gas composition and density during the chemoresponse trials. S_aO_2 was monitored throughout the testing period (Hewlett-Packard, 47201A Oximeter). The oximeter was calibrated according to the published instructions immediately before the chemoresponse

testing began and again halfway through the chemoresponse determinations. The S_aO_2 signal was channeled through the A/D board and into a personal computer where appropriate offset and scale factors were applied and S_aO_2 was displayed in real time. Every effort was made to prevent the subjects from being aware of changes in inspired gas composition during all determinations. Subjects were allowed to adjust to the apparatus for five to ten minutes and when their $\dot{V}_E$, $P_{ET}O_2$, and $P_{ET}CO_2$ had stabilized, data collection commenced.

Hypercapnic Chemoresponse

The technique used for the determination of the hypercapnic peripheral chemoresponse was modified from that previously reported by another author (32). The gas mixture used was approximately 13% CO_2, 21% O_2 and 66% N_2. After a minimum of 30 seconds of pre-stimulus data had been collected, subjects were switched to the hypercapnic gas mixture using the 4-way valve for one breath and then immediately back to room air. Data collection continued for approximately 60 seconds. A period of three to five minutes separated each of a minimum of five repeated trials.

The hypercapnic chemoresponse for each subject was determined in the following manner. The control $\dot{V}_I$ was calculated as the mean $\dot{V}_I$ of the five breaths immediately preceding the stimulus breath. The stimulus $\dot{V}_I$ was chosen as the highest single breath $\dot{V}_I$ recorded within 20 seconds of the stimulus breath. The control $P_{ET}CO_2$ was calculated as the mean value during the 30 second pre-stimulus period. The trial response was calculated as the ratio of the difference between the control $\dot{V}_I$ and the stimulus $\dot{V}_I$ to the difference between the control $P_{ET}CO_2$ and the $P_{ET}CO_2$ of the stimulus breath. The individual subject response was calculated as the mean of the five trial responses.

Hyperoxic Chemoresponse

The technique used for the determination of the hyperoxic peripheral chemoresponse was modified from that previously reported by another author (47). The gas mixture used was 100% O_2. After a minimum of 30 seconds of pre-stimulus data had been collected, subjects were switched to the hyperoxic gas using the 4-way valve. During resting studies subjects breathed the hyperoxic gas for 20 seconds (usually three breaths). During exercise studies subjects breathed the hyperoxic gas for the same number of breaths as they had in the resting studies. Once the period of hyperoxic gas breathing was completed subjects again inspired room air. Data collection continued for approximately 60 seconds. A period of three to five minutes separated each of a minimum of five repeated trials.

The hyperoxic chemoresponse for each subject was determined in the following manner. The control $\dot{V}_I$ was calculated as the mean $\dot{V}_I$ over the 30 second, pre-stimulus period. After hyperoxic breathing had begun $\dot{V}_I$ data was smoothed using a three breath moving mean. An individual subject response was calculated as the ratio of the lowest three breath $\dot{V}_I$ value averaged across trials to the average control period $\dot{V}_I$ value.

Saturation

For both the hypercapnic and hyperoxic responses the pre-stimulus S_aO_2 was determined in the same manner. For each trial the S_aO_2 was determined to be the mean value of the fifteen seconds immediately preceding the stimulus breath or breaths. The subject S_aO_2 was calculated as the mean of the five trial S_aO_2 values.

STATISTICAL ANALYSIS

The Students' T-test was used to compare group means of the descriptive subject data. The hypercapnic and hyperoxic responses as well as the pre-stimulus S_aO_2 values were analyzed as 2 x 4 RMANOVA's. In addition, the correlation between both sets of peripheral chemoresponse data and their associated pre-stimulus S_aO_2 was determined with linear regression analysis. The level of significance for all statistical comparisons was set at $p = 0.05$.

RESULTS

SUBJECT SELECTION

A total of 36 male cyclists were recruited for the study through advertisements in the Cycling British Columbia newsletter, and through word of mouth from previous subjects. Of the initial 36 subjects, 2 were excluded from further study because their results in the pulmonary function tests were substantially below predicted, 10 were excluded because their $\dot{V}_{O_2max}$ was less than 5.00 $L \cdot min^{-1}$ or 60.0 $mL \cdot min^{-1} \cdot kg^{-1}$, and 12 were excluded because either they did not satisfy the S_aO_{2max} criteria or the were not needed as the group they qualified for was complete. Using the criteria, $S_aO_{2max} \leq 91.0$ %, the first six subjects accepted into the study qualified for the low S_aO_{2max} (LOS) group. The reported incidence of exercise induced arterial hypoxemia of 52 % in highly trained endurance athletes (39, 42) makes this a highly unlikely occurrence. However, at least three of the subjects selected for the LOS group had been examined previously for exercise induced arterial hypoxemia in our lab and had tested positive. Based upon the reported incidence of exercise induced arterial hypoxemia in highly trained endurance athletes only twelve more subjects should have been required to complete the selection of subjects for the NOS group. This, however, was not the case. The upper limit of the S_aO_{2max} criteria, $S_aO_{2max} \geq 94.0$ %, was originally chosen in an attempt to create as large a separation between subjects in the two groups as possible. Using this criteria to select subjects for the normal S_aO_{2max} (NOS) group resulted in only two subjects qualifying for that group out of the next fifteen subjects tested. A number of the subjects not qualifying for the NOS group did qualify for the LOS group but were not studied further as that group was complete. The remaining subjects had S_aO_{2max} values which

fell between the upper and lower limits of the S_aO_{2max} selection criteria. The upper limit of the S_aO_{2max} criteria was then lowered to $S_aO_{2max} \geq 93.0$ % (1 SD below the mean decrease in S_aO_2 found in normal subjects during exercise (39)) and three more subjects were found for the NOS group as well as one additional subject for the LOS group. The additional LOS subject was accepted because he demonstrated the highest degree of exercise induced arterial hypoxemia of all subjects tested. Initially it was thought that the apparent low number of subjects qualifying for the LOS group was indicative of an incidence of exercise induced arterial hypoxemia that was much higher than previously reported. However, examination of data from all subjects indicated an incidence of exercise induced arterial hypoxemia in subjects with $\dot{V}_{O_2max} \geq 5.00$ L·min^{-1} or 60.0 mL·min^{-1}·kg^{-1} of 31 % (8 subjects out of 26) which is substantially lower than values reported by Powers et al. (39) and is slightly lower than values reported in more recent studies (41, 42) even though the subjects in this study had lower $\dot{V}_{O_2max}$ values. Interestingly, two subjects that did not satisfy the fitness selection criteria ($\dot{V}_{O_2max}$ = 4.69 ± 0.19 L·min^{-1}, 53.8 ± 3.5 mL·min^{-1}·kg^{-1}) did demonstrate mild exercise induced arterial hypoxemia (S_aO_{2max} = 90.3 ± 0.1 %). Individual subject descriptive data and $\dot{V}_{O_2max}$, peak power, S_aO_{2max}, and $\dot{V}_{O_2TH}$ data for subjects not qualifying for complete study can be found in Appendix D.

Of the subjects selected for complete study, six were competitive road cyclists (LOS, three; NOS, three), three were competitive off-road cyclists (LOS, one; NOS, two), one was a competitive duathlete (LOS), one was a recreational triathlete (LOS), and one was a recreational athlete who had previously competed as an Olympic class oarsman (LOS).

ANTHROPOMETRIC DATA

Subjects in both groups were similar in height, weight, and body surface area (BSA) (Table 1). Individual subject values for all descriptive variables can be found in Table 6.

Table 1 Age, height, mass and body surface area of subjects, group data.

GROUP	AGE (yrs)	HEIGHT (cm)	MASS (kg)	BSA (m^2)
LOS (n=7)	28.9 ± 8.1	180.1 ± 5.9	74.9 ± 7.3	1.94 ± 0.10
NOS (n=5)	25.4 ± 5.3	185.3 ± 5.0	79.0 ± 2.5	2.03 ± 0.06

Values are means ± SD. LOS, low oxygen saturation; NOS, normal oxygen saturation.

RESTING PULMONARY FUNCTION DATA

Resting pulmonary function data were compared with normative values generated by the testing apparatus. Subjects in both groups had similar values for FVC, FEV_1, FEV_1/FVC, and MVV. Subjects in the LOS group had significantly higher FEF_{max} values than NOS subjects ($t_{10} = 2.24$, $p = 0.025$). Individual subject data can be found in Table 7. All subjects demonstrated normal or supra-normal pulmonary function. The highest values for any pulmonary function variable, when compared to individual predicted values, were found in the FEF_{max} data with values ranging as high as 152% of predicted.

Table 2 Resting Pulmonary Function, group data.

GROUP	FVC (L) (% Pred.)	FEV_1 (L) (% Pred.)	FEV_1/FVC	FEF_{max} ($L \cdot sec^{-1}$) (% Pred.)	MVV ($L \cdot min^{-1}$) (% Pred.)
LOS (n=7)	5.76 ± 0.78	4.51 ± 0.65	0.79 ± 0.09	11.25 ± 1.44 *	197 ± 16
	104 ± 12	98 ± 7		132 ± 14	109 ± 10
NOS (n=5)	6.60 ± 0.63	4.95 ± 0.65	0.75 ± 0.07	9.49 ± 1.18	188 ± 27
	107 ± 4	97 ± 6		107 ± 11	104 ± 12

Values are means ± SD. LOS, low oxygen saturation; NOS, normal oxygen saturation. Value indicated by (*) is significantly higher than NOS ($p < 0.05$).

MAXIMAL CYCLE ERGOMETRY

There were no significant differences between groups in $\dot{V}_{O_2max}$, or peak power output (Table 3). Results from the $\dot{V}_{O_2max}$ test for all subjects are listed in Table 8. The mean $\dot{V}_{O_2max}$ of all subjects was 5.08 ± 0.32 $L \cdot min^{-1}$ or 66.6 ± 4.7 $mL \cdot min^{-1} \cdot kg^{-1}$, indicating the high training status of the subjects. Values for $\dot{V}_{O_2max}$ for subjects in both groups are comparable to data reported in previous studies (20, 41) but are lower, on average, than those reported by Dempsey et al. (11).

There was substantial overlap in the range of $\dot{V}_{O_2max}$ for subjects in each group (LOS, 59.6 - 74.5; NOS, 62.6 - 69.9 $mL \cdot min^{-1} \cdot kg^{-1}$). As a result there was not a significant relationship between $\dot{V}_{O_2max}$ and S_aO_{2max} in these subjects ($r = 0.138$, $F_{(1,10)reg} = 0.193$, $p = 0.669$). This remained the case when subjects were separated into groups (LOS, $r = 0.392$, $F_{(1,10)reg} = 0.909$, $p = 0.384$; NOS, $r = 0.592$, $F_{(1,10)reg} =$

1.621, p = 0.293). These results are contrary to those reported previously by other authors (39, 42).

Table 3 $\dot{V}O_2max$, peak power output, and S_aO_2max of subjects, group data.

GROUP	$\dot{V}O_2max$ ($L \cdot min^{-1}$)	$\dot{V}O_2max$ ($mL \cdot min^{-1} \cdot kg^{-1}$)	Peak Power (Watts)	S_aO_2max (%)
LOS (n=7)	4.96 ± 0.26	66.8 ± 6.0	458 ± 31	89.9 ± 0.9 *
NOS (n=5)	5.24 ± 0.34	66.4 ± 2.9	453 ± 23	93.4 ± 0.4

Values are means ± SD. S_aO_2max is lowest arterial oxygen saturation during the maximal cycle ergometer test. Value denoted by (*) is significantly lower than NOS ($p < 0.05$).

The $\dot{V}O_{2TH}$ of subjects in the LOS group was higher than in the NOS group although the difference did not reach statistical significance ($t_{10} = 1.791$, $p = 0.052$) (Table 4). As a result LOS subjects had higher power outputs at their $\dot{V}O_{2TH}$ than NOS subjects ($t_{10} = 3.346$, $p = 0.004$). Individual subject values for $\dot{V}O_{2TH}$ are listed in Table 9.

Table 4 $\dot{V}O_{2TH}$, and power output at $\dot{V}O_{2TH}$, group data.

Group	$\dot{V}O_{2TH}$ ($L \cdot min^{-1}$)	$\dot{V}O_{2TH}$ ($mL \cdot min^{-1} \cdot kg^{-1}$)	Power at $\dot{V}O_{2TH}$ (Watts)
LOS (n=7)	3.26 ± 0.14	46.0 ± 4.7	300 ± 26 *
NOS (n=5)	3.31 ± 0.11	42.0 ± 1.8	259 ± 9

Values are means ± SD. Value denoted by (*) is significantly higher than NOS ($p < 0.05$).

EXERCISE WORKLOADS

The workloads for the chemoresponse trials were selected for two reasons: to extend the measurement of peripheral chemoresponsiveness during exercise to the highest intensities possible, hoping to elicit a hypoxemic response in the LOS subjects, and to choose as the highest workload an intensity that would allow completion of the peripheral chemoresponse data collection. Thus, the highest workload that could be practically used corresponded to the power output at $\dot{V}_{O_2TH}$. Since this was thought to average around 75 % of $\dot{V}_{O_2max}$ in highly trained endurance cyclists the absolute workloads of 25 % and 50 % of $\dot{V}_{O_2max}$ and $\dot{V}_{O_2TH}$ were chosen for the lower exercise levels. This would have resulted in a roughly linear increase in power output from the very low power output to the moderate power output exercise levels. The power outputs in both LOS and NOS increased in a linear fashion from the very low power output to moderate power output exercise levels ($F_{(1,10)lin} = 846.883$, $p < 0.001$). However, not only was the rate of increase in power output in the NOS group lower than that of the LOS group ($F_{(1,10)lin\ int} = 14.756$, $p = 0.003$), but the pattern of change in the increase in power output was different in the two groups ($F_{(3,30)int} = 12.858$, $p < 0.001$) (Figure 7). Specifically, subjects in both groups had similar power outputs at the very low power output and low power output exercise levels, but the NOS subjects had a substantially lower power output at moderate power output exercise level than the LOS subjects (Table 5). This was because the $\dot{V}_{O_2TH}$ of LOS subjects was higher than NOS subjects and as a result the moderate power output workload, which was approximately the ventilatory threshold workload, was higher in the LOS subjects. Consequently, the two lower workloads were effectively absolute workloads while the highest workload was a relative workload. The

workloads derived by regression analysis for each subject, based upon their individual $\dot{V}_{O_2}$/power output relationship, are listed in Table 10.

Table 5 Power outputs maintained during chemoresponse tests, group data.

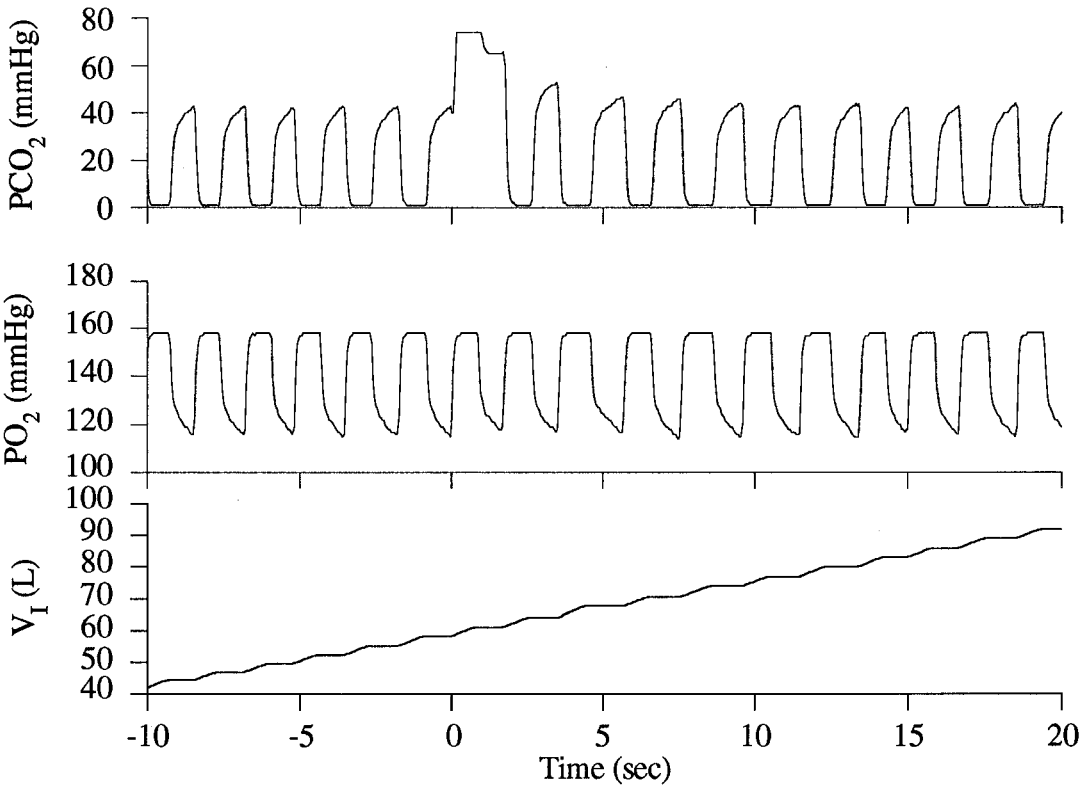
	Exercise Level		
GROUP	VLPO	LPO	MPO
LOS (n=7)	70 ± 11	194 ± 19	272 ± 28
NOS (n=5)	77 ± 13	199 ± 10	232 ± 11

Units are Watts. Values are means ± SD. LOS, low oxygen saturation; NOS, normal oxygen saturation. VLPO, very low power output; LPO, low power output; MPO, moderate power output.

HYPERCAPNIC PERIPHERAL CHEMORESPONSE

The results of a typical hypercapnic peripheral chemoresponse trial can be seen in Figure 1a and Figure 1b.

Figure 1a PCO_2 , PO_2 , and V_I of single hypercapnic peripheral chemoresponse.

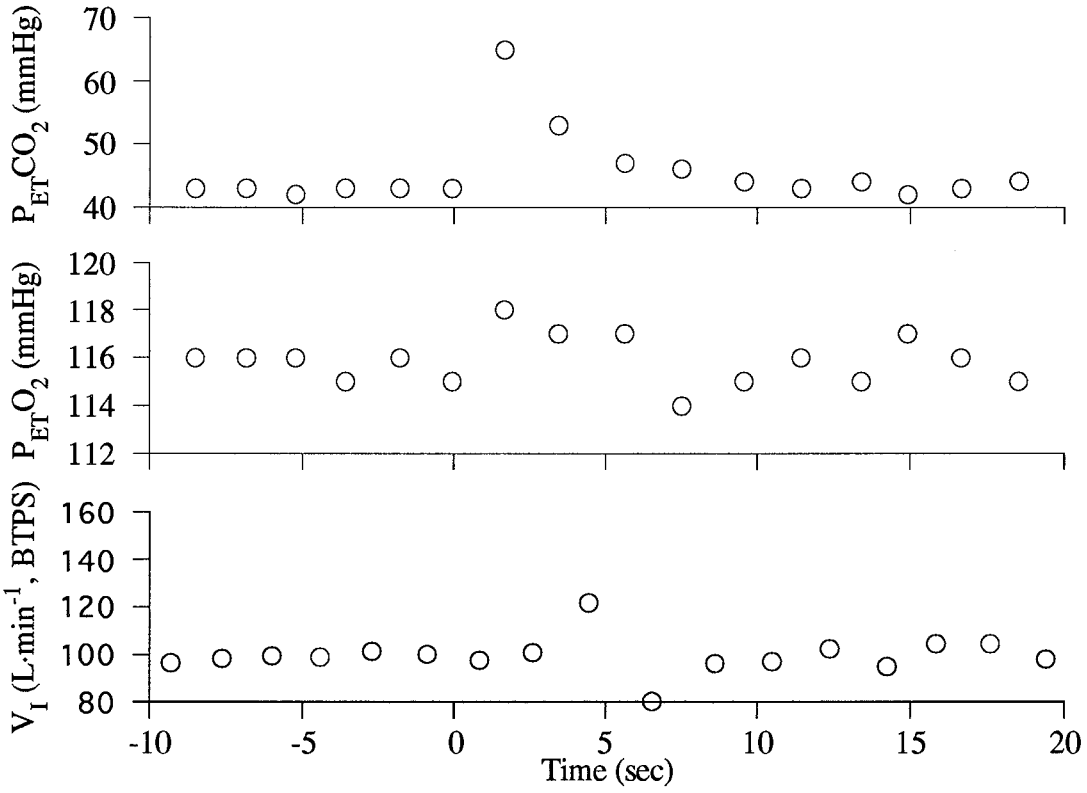


Subject, PT. Exercise level, MPO. Traces are offset and scaled data sampled at 20 Hz. Stimulus breath occurs at t=0.

The response shown in Figure 1a and Figure 1b is of an LOS subject at the moderate power output exercise intensity. The offset and scaled analyzer output traces are

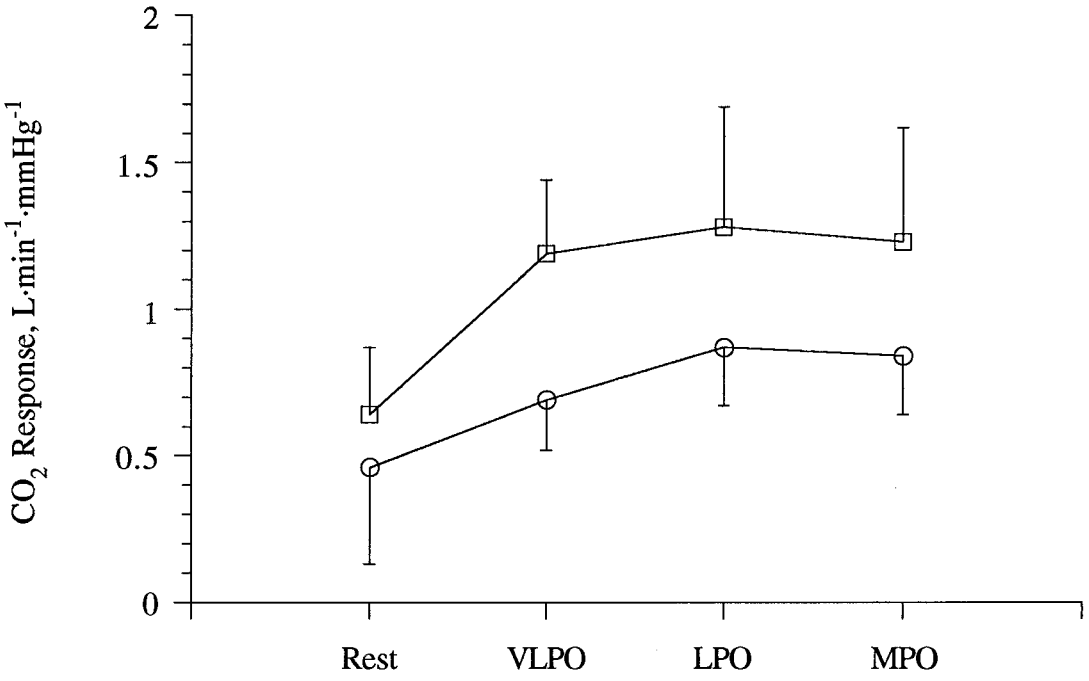
shown in Figure 1a and the breath-by-breath values derived from the offset and scaled traces are shown in Figure 1b. In these figures the switching of inspired gas from room air to the test gas occurs at t=0. Prior to the stimulus breath are shown five breaths used to calculate the pre-stimulus control $\dot{V}_I$, and the pre-stimulus control $P_{ET}CO_2$. Following the stimulus breath are shown the breaths occurring in the next twenty seconds, from which the breath with the highest $\dot{V}_I$ was chosen as the response breath. The response breath in this particular trial occurred two breaths after the stimulus breath (less than 5 seconds after the stimulus). This was the case in most trials with the response breath being the second or third breath after the stimulus breath, the time decreasing with increasing exercise intensity. At lower exercise levels, or at rest, the V_I trace shows an obvious increase in slope following the stimulus breath. At the higher exercise levels this slope increase is less visible in the raw V_I trace and is only seen in the breath-by-breath plot of $\dot{V}_I$.

Figure 1b $P_{ET}CO_2$, $P_{ET}O_2$, and $\dot{V}_I$ for a single hypercapnic peripheral chemoresponse.



Exercise level, MPO. Subject, PT. Plot shows values extracted from raw data shown in Figure 1a. $\dot{V}_I$ calculated from V_I and f_R on a breath-by-breath basis.

Figure 2 Hypercapnic peripheral chemoresponse at various exercise intensities, group data.

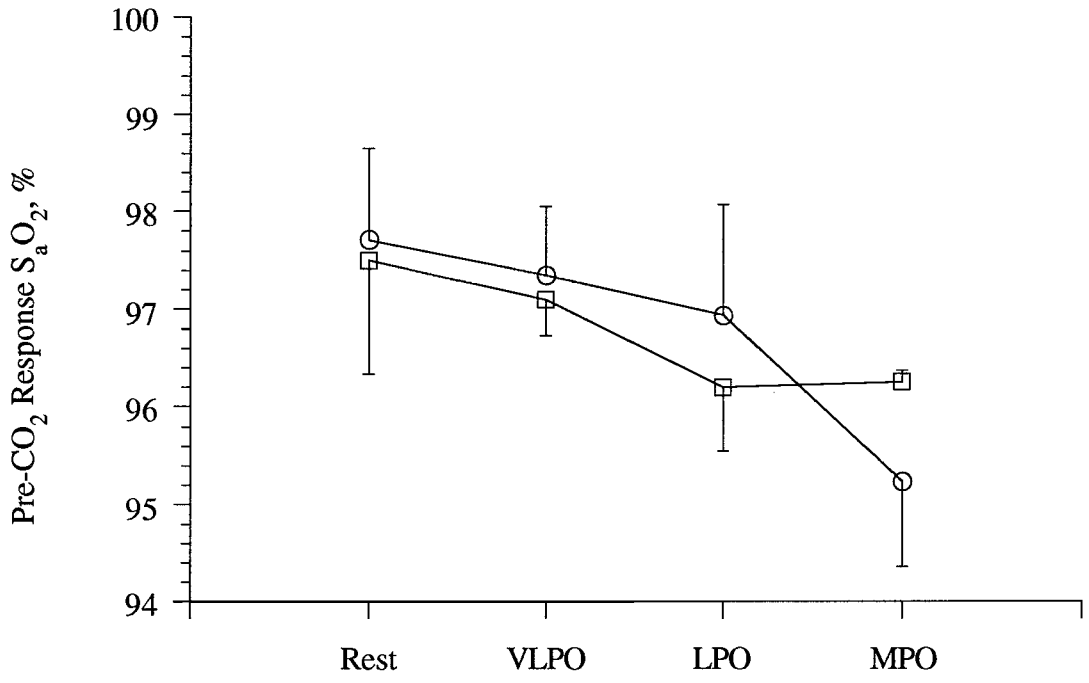


Values are means ± SD. Open circles, LOS; Open squares, NOS. VLPO, very low power output; LPO, low power output; MPO, moderate power output.

The hypercapnic peripheral chemoresponse was significantly higher in NOS than in LOS ($F_{(1,10)group} = 13.652$, $p = 0.004$) and it increased significantly in both groups ($F_{(3,30)trials} = 10.446$, $p < 0.001$) from rest to exercise (Figure 2). In addition, while hypercapnic peripheral chemoresponse as a function of exercise level had a significant linear component in both groups ($F_{(1,10)lin} = 13.413$, $p = 0.004$), there was also a significant plateauing of hypercapnic peripheral chemoresponse near the higher

workloads in both groups ($F_{(1,10)quad} = 8.197$, $p = 0.017$). Individual subject, averaged, hypercapnic chemoresponses are listed in Table 11.

Figure 3 Pre-CO_2 response S_aO_2 at various exercise intensities, group data.



Values are means ± SD. Open circles, LOS; Open squares, NOS. VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Pre-Stimulus Arterial Hemoglobin Saturation

The pre-stimulus S_aO_2 during hypercapnic peripheral chemoresponse trials was not different in LOS and NOS averaged across exercise levels ($F_{(1,10)group} = 0.019$, $p = 0.894$), however a significant fall in S_aO_2 was seen in both groups ($F_{(3,30)trials} = 15.12$,

$p < 0.0001$). The fall in S_aO_2 in the LOS group was larger than that of the NOS group ($F_{(3,30)int} = 3.213$, $p = 0.037$) and it occurred mostly from the low power output to moderate power output exercise intensities. The fall in S_aO_2 in both groups was almost entirely a linear function of increasing exercise intensity ($F_{(1,10)lin} = 34.299$, $p < 0.0001$) with the more pronounced decrease in the LOS group at the moderate power output exercise intensity ($F_{(1,10)quad\ int} = 6.596$, $p = 0.028$) accounting for any deviation from linearity.

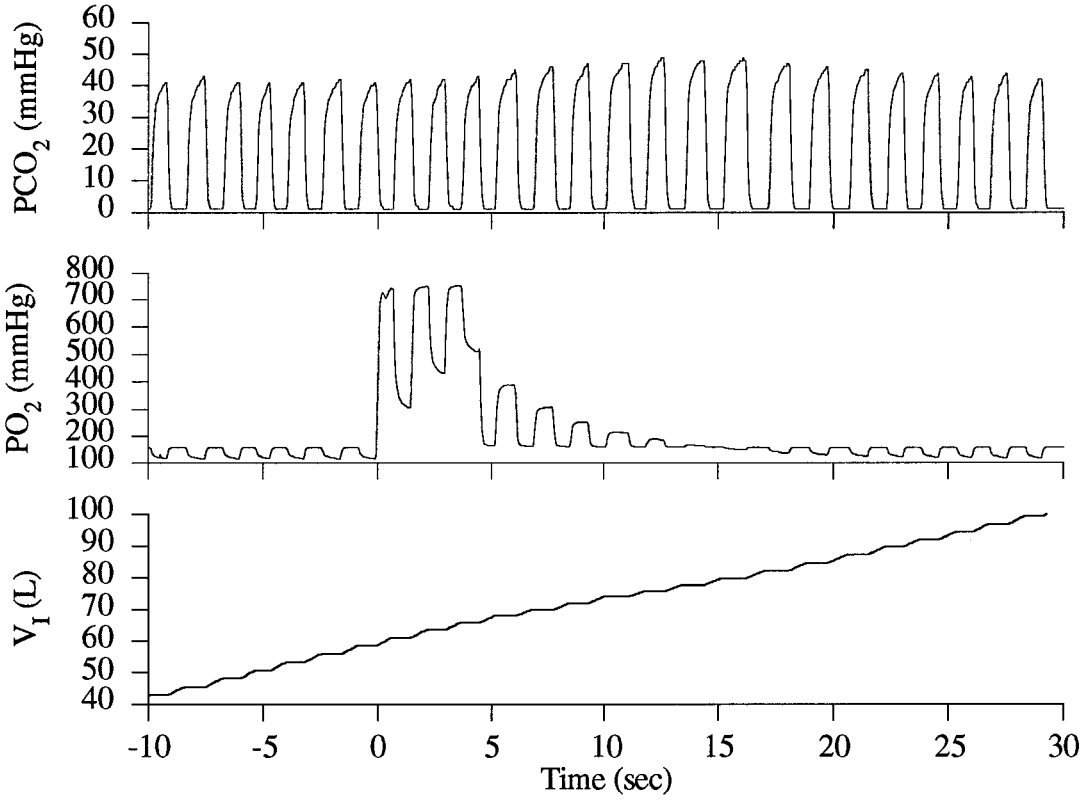
Hypercapnic Peripheral Chemoresponse and Pre-Stimulus Arterial Hemoglobin Saturation

There was not a significant linear relationship between hypercapnic peripheral chemoresponsiveness and pre-stimulus S_aO_2 in either group of subjects (LOS, $r^2 = 0.115$, $p = 0.078$; NOS, $r^2 = 0.097$, $p = 0.181$).

HYPEROXIC CHEMORESPONSE

The results of a typical hyperoxic peripheral chemoresponse trial can be seen in Figure 4a and Figure 4b.

Figure 4a PCO_2, PO_2, and V_I of a single hyperoxic peripheral chemoresponse.

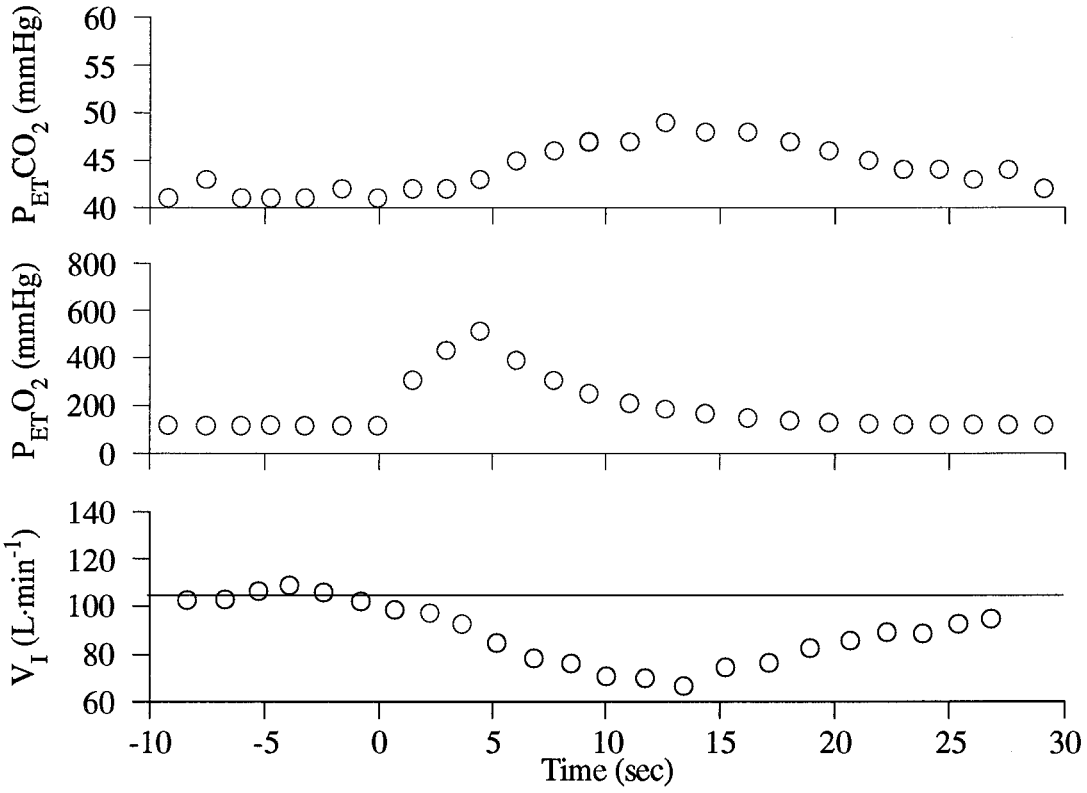


Exercise level, MPO; subject, PT. Plot shows offset and scaled data sampled at 20 Hz. V_I calculated in real-time from inspiratory flow rate.

The response shown in Figure 5a and Figure 5b is of an LOS subject at the moderate power output exercise intensity. The offset and scaled analyzer output traces are

shown in Figure 5a and the breath-by-breath values derived from the offset and scaled traces are shown in Figure 5b. In these figures the switching of inspired gas from room air to the test gas occurs at t=0. Prior to the stimulus breath are shown a number of breaths from the 30 second pre-stimulus control period used to calculate the pre-stimulus control $\dot{V}_I$. Following the stimulus breath are shown the breaths occurring in the next thirty seconds, from which the breath with the lowest $\dot{V}_I$ is chosen as the response breath. At lower exercise levels, or at rest, the V_I trace shows an obvious decrease in slope following the stimulus breath. At the higher exercise levels this slope decrease is less visible in the V_I trace and is only seen in the breath-by-breath plot of $\dot{V}_I$.

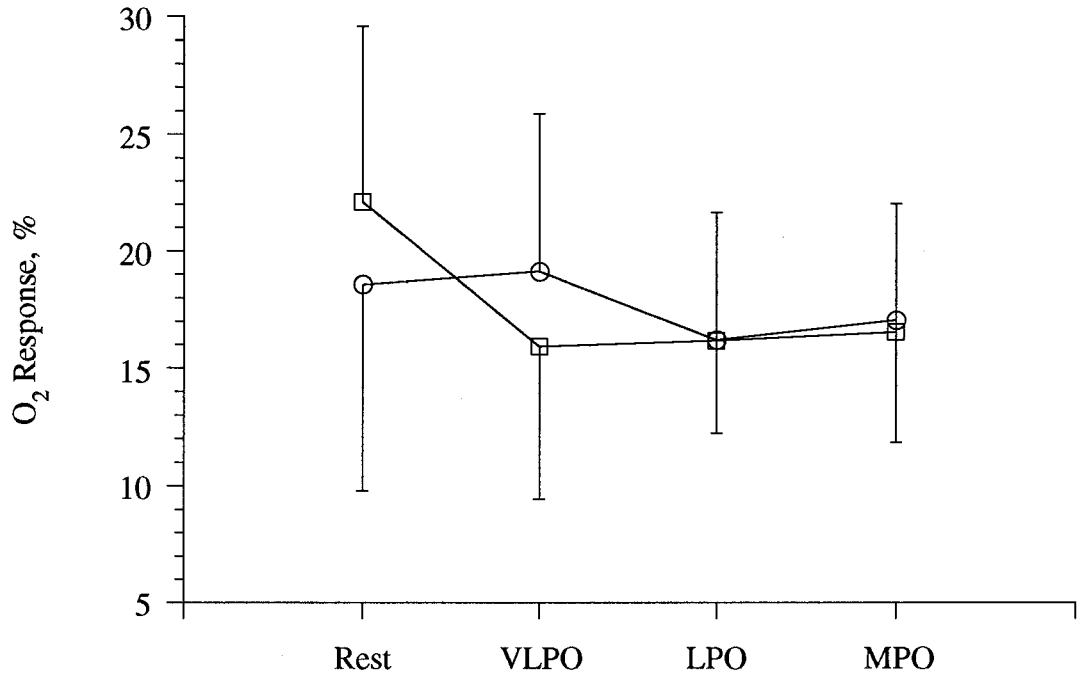
Figure 4b $P_{ET}CO_2$, $P_{ET}O_2$, and $\dot{V}_I$ for a single hyperoxic peripheral chemoresponse.



Exercise level, MPO; subject, PT. Plot shows values extracted from offset and scaled data shown in Figure 5a. $\dot{V}_I$ calculated from V_I and f_R on a breath-by-breath basis.

The hyperoxic chemoresponse was not significantly different either between groups or across exercise levels ($F_{(1,10)group} = 0.000$, $p = 0.988$, $F_{(3,30)trials} = 2.152$, $p = 0.115$), nor was there a significant interaction effect ($F_{(3,30)int} = 1.224$, $p = 0.318$) (Figure 5). Individual subject, averaged, hyperoxic chemoresponses are listed in Table 16.

Figure 5 Hyperoxic peripheral chemoresponse at various exercise intensities, group data.



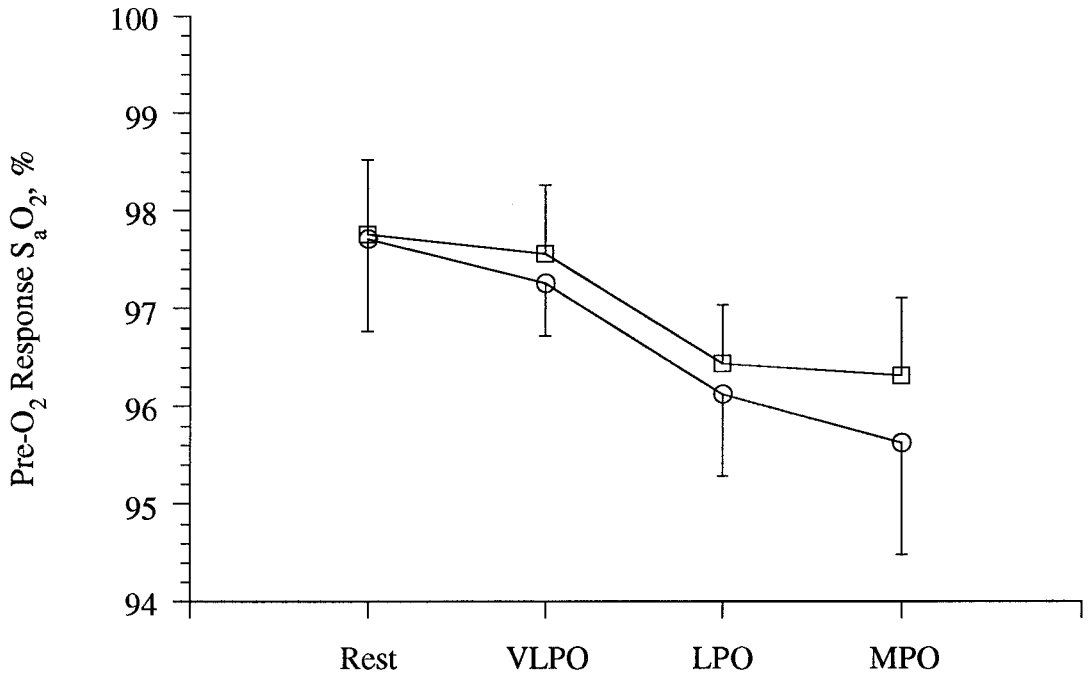
Values are means ± SD; open circles, LOS; open squares, NOS. VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Pre-Stimulus Arterial Hemoglobin Saturation

The pre-stimulus S_aO_2 during hyperoxic peripheral chemoresponse trials was not different in LOS and NOS ($F_{(1,10)group} = 0.966$, $p = 0.349$) averaged across exercise levels, however a significant fall in S_aO_2 was seen in both groups ($F_{(3,30)trials} = 18.769$, $p < .0001$) (Figure 6). The fall in S_aO_2 in the LOS group was not larger than that of the NOS group ($F_{(3,30)int} = 0.456$, $p = 0.715$). The fall in S_aO_2 in both groups was almost

entirely a linear function of increasing exercise intensity ($F_{(1,10)lin} = 36.276$, $p < .0001$) with a significant inverted sigmoid function ($F_{(1,10)cubic} = 11.828$, $p = 0.006$) accounting for any deviation from linearity. The pre-stimulus S_aO_2 data for all subjects during hyperoxic peripheral chemoresponse trials are shown in Table 18.

Figure 6 Pre-O_2 response S_aO_2 at various exercise intensities, group data.



Values are means ± SD; open circles, LOS; open squares, NOS. VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Hyperoxic Peripheral Chemoresponse and Pre-Stimulus Arterial Hemoglobin Saturation

There was not a significant linear relationship between hyperoxic peripheral chemoresponse and pre-stimulus S_aO_2 in either group of subjects (LOS, $r^2 = 0.015$, $p = 0.540$; NOS, $r^2 = 0.002$, $p = 0.846$).

DISCUSSION

Exercise induced arterial hypoxemia occurs in 40 to 50 % of highly trained endurance athletes (39, 42) and has a detrimental effect on both $\dot{V}_{O_2max}$ and exercise performance (27, 42). The primary mechanisms suggested to be responsible for exercise induced arterial hypoxemia are veno-arterial shunt, diffusion disequilibrium secondary to increased pulmonary transit time or pulmonary edema, $\dot{V}_A$:$\dot{Q}_C$ heterogeneity (11, 19, 49) and relative hypoventilation (11, 30). A substantial amount of research has been undertaken to elucidate the proportional importance of these mechanisms with somewhat contradictory results. Much of the work investigating the relative importance of hypoventilation in exercise induced arterial hypoxemia has involved only description or comparison of the ventilatory responses of the subjects who do and do not demonstrate exercise induced arterial hypoxemia. No studies have examined the ventilatory control mechanism directly and related any observations made to the incidence of exercise induced arterial hypoxemia. As a result some authors have excluded the hypoventilation mechanism as playing a major role in the development of exercise induced arterial hypoxemia (42).

This study represents the first attempt to measure the peripheral chemoresponsiveness to hypercapnia and hyperoxia, at rest and during very light to moderate exercise, in highly trained endurance athletes. The peripheral chemoresponsiveness of these highly trained endurance athletes is compared with results obtained from previous studies on trained and untrained individuals at rest and during exercise. In addition, the relationship between peripheral chemoresponsiveness and exercise induced arterial hypoxemia is investigated by comparing the peripheral

chemoresponsiveness of highly trained endurance athletes who do and do not demonstrate exercise induced arterial hypoxemia.

RESTING PULMONARY FUNCTION, MAXIMAL EXERCISE TESTS, AND SUBJECT SELECTION

The subjects in this study all demonstrated pulmonary function values within predicted normal ranges. Interestingly, it was common for subjects to be significantly higher than predicted on FEF_{max} and MVV, while at the same time values for FEV_1 and FEV_1/FVC were only normal or slightly sub-normal. It is possible that the very high FEF_{max} values, as high as 152 % of predicted, were simply related to the superior development of the thoracic musculature in these athletes. However, many subjects who had very high FEF_{max} values also had mid-expiratory flow rates that were substantially below predicted. All subjects reached at least 90 % of their MVV during the incremental cycle ergometer test.

Values for $\dot{V}_{O_2max}$ for subjects in this study are comparable to data reported in some previous studies (20, 41) but are lower, on average, than those reported by Dempsey et al. in 1984 (11). Contrary to previous reports (39), no relationship was found between $\dot{V}_{O_2max}$ and S_aO_2max in the subjects in this study either as a whole or when divided into groups based on the presence of exercise induced arterial hypoxemia. The incidence of exercise induced arterial hypoxemia in the highly trained endurance athletes who completed this study was 58 %. This result overestimates the actual incidence of exercise induced arterial hypoxemia observed in all subjects completing the maximal cycle ergometer test as most subjects completing that test were not studied further because: 1) they did not pass the pulmonary function criteria, 2) they did not pass the

$\dot{V}_{O_2max}$ criteria, or 3) they qualified for the LOS group but that group was already full. The incidence of exercise induced arterial hypoxemia in all subjects meeting the $\dot{V}_{O_2max}$ criteria for inclusion in the study was only 38 %, which agrees with lower incidences reported (41). There were two subjects who did not meet the $\dot{V}_{O_2max}$ criteria that did demonstrate exercise induced arterial hypoxemia. They would have been categorized as moderately trained in the previous study (39) that reported no cases of exercise induced arterial hypoxemia in subjects of similar $\dot{V}_{O_2max}$.

Although subjects in both groups demonstrated similar levels of aerobic power at maximal exercise, the aerobic power at the ventilatory threshold of the LOS subjects was higher than the NOS subjects. As a result the moderate power output exercise intensity was a relative work load while the very low power output and low power output exercise intensities were both relative and absolute work loads in these subjects. Comparison of the exercise intensities attained in this study with similar studies of peripheral chemoresponsiveness (30, 32, 21, 22, 47, 51) confirm that not only were higher absolute power outputs attained with these highly trained endurance athletes but higher relative exercise intensities were attained as well.

MEASUREMENT OF PERIPHERAL CHEMORESPONSES

Computerization of the techniques of McClean et al. (1988) and Stockley (1978) made the collection and analysis of data during both resting and the three exercise determinations of peripheral chemoresponsiveness to hypercapnia and hyperoxia possible. The automation and computerization of the data collection and analysis also permitted more reliable determination of valid responses than in the previous studies

since errors in the calculation of $\dot{V}_I$ from the slope of a chart recording of V_I were eliminated.

Hypercapnic Peripheral Chemoresponse

At the time that the study was undertaken the technique described by McClean et al. (1988) was the only technique that enabled measurement of the peripheral chemoresponse to hypercapnia during exercise. During the hypercapnic peripheral chemoresponse trials it was impossible to keep the subjects completely unaware of the beginning of CO_2 breathing. At an inspired fraction of 13 % the level of CO_2 in the test gas was sufficiently high to be tasted by most subjects. A sharp increase in the peak and mean expiratory flow rates during the second and third breaths after the stimulus breath, in conjunction with reports from some subjects of a perceived need to exhale forcefully, confirmed that the administration of the stimulus was not completely blind. However, a number of factors suggest that the influence of these cortical perceptions on the peripheral chemoresponse to hypercapnia, although unknown, is probably small: 1) the peripheral chemoresponse to hypercapnia was determined from $\dot{V}_I$ and not $\dot{V}_E$ and the cortical perceptions would not be likely to increase the inspiratory drive, 2) increases in the inspiratory flow rate were much smaller in proportion to those in expiratory flow rate, and 3) subjects were naive about which test gas they were receiving in what doses during any given chemoresponse trial.

The use of $P_{ET}CO_2$ to quantify the stimulus delivered to the carotid body chemoreceptor is based upon the assumption that there is a small and constant arterial to alveolar CO_2 difference. This has not been documented in the literature and could be a confounding factor, especially in subjects who likely suffer from some diffusion limitation of O_2. The fact that the exercise intensities used did not elicit exercise induced

arterial hypoxemia in any of the subjects suggests that if a significant arterial to alveolar CO_2 difference can exist it was not likely to be present in these studies.

Hyperoxic Peripheral Chemoresponse

Unlike during the hypercapnic peripheral chemoresponse tests, subjects were unaware when measurement of hyperoxic peripheral chemoresponsiveness took place. The test gas, although it was dry and was inspired for between 5 and 20 seconds, did not increase or decrease any sensations of dyspnea at rest or during exercise. Also, with the addition of on-line display of inspired and expired PO_2 and PCO_2 to the method of Stockley (47) evidence of hypoventilation in response to the hyperoxic stimulus could easily be detected facilitating the identification of valid responses.

The lack of isocapnic conditions during the hyperoxic chemoresponse tests results in a variable underestimation of the decrease in ventilation in response to hyperoxia at rest and during exercise. Thus caution is required when comparing data from this study with other studies where isocapnia was maintained.

EFFECT OF TRAINING STATUS ON PERIPHERAL CHEMORESPONSIVENESS

The hypercapnic peripheral chemoresponsiveness of the highly trained endurance athletes in this study was higher at rest (mean ± SD, 0.54 ± 0.30 $L \cdot min^{-1} \cdot mmHg^{-1}$) than values reported for healthy untrained males (mean ± SD, 0.38 ± 0.14 $L \cdot min^{-1} \cdot mmHg^{-1}$) (32). This is in agreement with data indicating that peripheral chemosensitivity to hypercapnia is higher in trained versus untrained individuals (25) but is contrary to reports of others documenting a decrease in chemosensitivity to hypercapnia in individuals following prolonged exercise training (35). The results of the second study were obtained using a CO_2 rebreathing technique in which both central and peripheral

chemoreceptive mechanisms are active. The results of the study by Miyamura and Ishida (35) are not in conflict with data from this study if, while peripheral chemoresponsiveness increases with training, central chemoresponsiveness decreases with training, the net result being an overall increase in chemoresponsiveness to hypercapnia.

The resting hyperoxic peripheral chemoresponsiveness of subjects in this study (mean ± SD, 20.0 ± 8.1 %) is similar to previously reported values in a group of athletes of similar aerobic capacity (mean ± SD, 22 ± 2 %) (31) and is slightly higher than a group of healthy, normal subjects (mean ± SE (n=35), 16.2 ± 2.6 %) (47). The difference between the data in this study and the data of Stockley (1978) is not significant (t_{45} = 0.813, p = 0.210) and would suggest that there is no difference between trained and untrained individuals in the resting contribution to normoxic $\dot{V}_E$ of hypoxic sensitivity. This seems intuitive because at rest both trained and untrained individuals have the same S_aO_2 and P_aO_2.

EFFECT OF EXERCISE ON PERIPHERAL CHEMORESPONSIVENESS

Subjects in this study demonstrated an increase in peripheral chemoresponsiveness to hypercapnia associated with exercise supporting previous reports of an augmentation of peripheral chemoresponsiveness to hypercapnia during exercise (21, 22). Further, this data indicates that on transition from very light to moderate exercise the rate of increase in peripheral chemosensitivity decreases with increasing exercise intensity. It would seem that as exercise intensity increases approaching and exceeding the ventilatory threshold peripheral chemosensitivity to hypercapnia plays a less important role in the development of exercise hyperpnea.

As others have reported (31, 47) this study did not demonstrate a statistically significant change in hyperoxic peripheral chemoresponsiveness with increasing exercise intensity. A previous report (51) indicated that hyperoxic chemoresponsiveness was augmented by exercise, however, the observations in that study were based on an extrapolation of $\dot{V}_E$ to an infinitely high P_aO_2 and are questionable in light of the more recent work by the same group (31).

PERIPHERAL CHEMORESPONSIVENESS AND EXERCISE INDUCED ARTERIAL HYPOXEMIA

In the present study the peripheral chemosensitivity to hypercapnia was lower in subjects who demonstrated exercise induced arterial hypoxemia. This effect cannot be attributed to a difference in trained status because subjects in both groups had similar $\dot{V}_{O_2max}$. Differences between the LOS and NOS subjects at the two low exercise intensities are not likely to be simple exercise effects because the subjects exercised at the same relative and absolute metabolic rate. At the moderate power output exercise level the LOS subjects were exercising at a higher metabolic rate relative to $\dot{V}_{O_2max}$, although both groups were exercising at their $\dot{V}_{O_2TH}$, and the difference in hypercapnic peripheral chemoresponsiveness present at the low power output exercise intensities was maintained. The pattern of change in peripheral chemoresponsiveness to hypercapnia as a function of increasing exercise intensity was the same in both LOS and NOS subjects. There seems to be a relationship between exercise induced arterial hypoxemia and the sensitivity of the peripheral chemoreceptors to hypercapnia.

The absence of a difference in hyperoxic peripheral chemoresponsiveness between LOS and NOS subjects indicates that, at the exercise intensities studied, there is

no relationship between hyperoxic peripheral chemoresponsiveness and exercise induced arterial hypoxemia. This is probably due to the fact that the moderate power output exercise intensity was not high enough to induce arterial hypoxemia in the LOS subjects and the baseline activation of the peripheral chemoreceptors to hypoxia was not different from NOS subjects. A relationship between hyperoxic peripheral chemoresponsiveness and exercise induced arterial hypoxemia may become apparent at higher workloads but this study has no data to support this hypothesis.

PERIPHERAL CHEMORESPONSIVENESS AND PRE-STIMULUS ARTERIAL HEMOGLOBIN SATURATION

No evidence was found to support the hypothesis that peripheral chemoresponsiveness was related to exercise S_aO_2. Although there was a difference in peripheral chemoresponsiveness to hypercapnia in LOS and NOS subjects there was no difference between groups in pre-stimulus S_aO_2 averaged across exercise intensities and peripheral chemoresponsiveness was not different in LOS and NOS subjects. Again, although subjects in the LOS group had lower pre-stimulus S_aO_2 values at the moderate power output exercise intensity, they did not demonstrate exercise induced arterial hypoxemia and this fact may have prevented the detection of a relationship between these variables.

IMPLICATIONS FOR VENTILATORY CONTROL

The ventilatory control mechanism suggested by some authors (48) consists of a feed-forward component that directs the initial response of the ventilatory system to increased CO_2 load, and a feed-back component that is responsible for correcting errors in the feed-forward portion of the control mechanism. Other authors have expanded this

model and suggest that the role of the peripheral chemoreceptors is to stabilize ventilation, effectively acting as a brake to the initial hyperventilation that accompanies the onset of exercise (3). Data from this study suggest that highly trained endurance athletes, who have higher hypercapnic peripheral chemoresponsiveness than untrained individuals, control this initial increase in ventilation more effectively, maintaining tighter control on P_aCO_2, pH_a and P_aO_2. It would seem that highly trained endurance athletes who demonstrate exercise induced arterial hypoxemia are less able to control their ventilation, they have lower hypercapnic peripheral chemoresponsiveness, under similar conditions and are more likely to experience wider variations in P_aCO_2, pH_a and P_aO_2 than individuals of similar aerobic capacity who do not demonstrate exercise induced arterial hypoxemia.

The mechanism of these changes in athletes with exercise induced arterial hypoxemia is unknown. It is possible that there are differences between these two groups of subjects in the physiologic response of the carotid bodies themselves, in the integration of afferent signals from the carotid bodies with other feed-back within the respiratory center or in the subsequent expression of this feed-back as a change in ventilation.

SUMMARY

The results of this study provide information which may help explain variations in the ventilatory response to exercise in athletes. Additionally, data from this study suggest a role of altered ventilatory control in highly trained endurance athletes who do and do not demonstrate exercise induced arterial hypoxemia. Further study is required to ascertain the specific causes of the reduced hypercapnic peripheral chemoresponsiveness

in highly trained endurance athletes who demonstrate exercise induced arterial hypoxemia.

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APPENDIX A

REVIEW OF LITERATURE

THE PULMONARY SYSTEM: A LIMITING FACTOR IN EXERCISE PERFORMANCE

There are a number of factors which are commonly considered to limit athletic performance in humans. However, which factor or combination of factors are most important remains controversial. The controversy revolves around the likelihood that as one moves along the continuum of aerobic power from untrained normal individuals ($\dot{V}_{O_2max}$ of approximately 40 $mL \cdot min^{-1} \cdot kg^{-1}$) to highly trained endurance athletes ($\dot{V}_{O_2max}$ of approximately 60 to 75 $mL \cdot min^{-1} \cdot kg^{-1}$) which of these potentially limiting factors becomes the most important for any specific sub-group of the population undoubtedly varies.

NORMAL, HEALTHY, UNTRAINED INDIVIDUALS

In healthy sedentary individuals, exercising at sea-level, the pulmonary system shows near perfect regulation of alveolar gases, distribution of alveolar ventilation ($\dot{V}_A$) and perfusion ($\dot{Q}_C$), and diffusion equilibrium in the lung at rest and during exercise. The capacity of the pulmonary systems of these individuals to extract oxygen from the atmosphere exceeds that of their cardiovascular and metabolic systems to deliver and use that oxygen (12). Maximal aerobic power ($\dot{V}_{O_2max}$) and therefore exercise performance are limited by maximal stroke volume, cardiac output, skeletal muscle vascularity and/or the oxidative capacity of the skeletal muscles (9) in these individuals . At sea level the pulmonary system is able to meet the demands placed on it for oxygen (O_2) extraction and carbon dioxide (CO_2) elimination during heavy exercise through a number of

mechanisms. Firstly, the hyperpnea of exercise ensures the maintenance of alveolar oxygen pressure (P_AO_2) above 110 mmHg maintaining arterial oxygen pressure (P_aO_2) near resting values (100 mmHg) and ensuring adequate elimination of CO_2 (2). Secondly, pulmonary capillary blood volume increases in a linear fashion up to 3 times its resting value with the 4 to 5-fold increase in pulmonary blood flow. This maintains red blood cell transit times necessary for equilibration of blood in the pulmonary capillaries with alveolar gas, a relatively uniform distribution of pulmonary blood flow and expansion of the alveolar-capillary surface area, and relatively low pulmonary vascular resistance (9). Finally, the lymphatic system is capable of adequately draining the pulmonary interstitial space of pulmonary extra vascular water. This prevents the lengthening of alveolar-capillary diffusion distances (8).

HIGHLY TRAINED, ENDURANCE ATHLETES

In highly trained endurance athletes the physiological adaptations of the cardiovascular system and of the oxidative capacities of the skeletal muscles, accompanied by the limited scope for adaptation in the pulmonary system, may result in the pulmonary system actually becoming the limiting factor in exercise performance (9, 43). In fact, many highly trained endurance athletes demonstrate a significant and reproducible decrease in P_aO_2 or arterial hemoglobin saturation (S_aO_2) during moderate to intense exercise. It is not entirely clear what level of S_aO_2 is required to maintain performance however some data suggests that measurable reductions in exercise performance begin to occur at S_aO_2's of less than 90% (27).

EXERCISE INDUCED ARTERIAL HYPOXEMIA

The reduction in P_aO_2 accompanying exercise was first reported by Harrop in 1919 (16) who observed a decrease in S_aO_2 from 95.6% at rest to 85.5% immediately following fifteen minutes of brisk exercise (heart rate = 140 beats·min^{-1}, f_R = 30 breaths·min^{-1}). More recent reports of reductions in P_aO_2 and/or S_aO_2, a phenomenon now commonly referred to as exercise induced arterial hypoxemia, are numerous (11, 20, 39, 42, 43).

DEFINITION OF EXERCISE INDUCED ARTERIAL HYPOXEMIA

Exercise induced arterial hypoxemia, although previously observed, was first defined by Powers et al. in 1988 (39) as a decrease in S_aO_2 from a resting value of approximately 97% to a value less than or equal 91% during exercise. This definition of a critical level of S_aO_2, allowed the authors to document the incidence and reproducibility of exercise induced arterial hypoxemia in highly trained endurance athletes (52%, r=0.95, $p<.05$). More recently the same authors have modified their definition of exercise induced arterial hypoxemia based on direct measurement of P_aO_2 in conjunction with measures of S_aO_2 (41). The incidence of exercise induced arterial hypoxemia is 40 % in highly trained endurance athletes using the new definition of a decrease in S_aO_2 of 4 % below resting S_aO_2.

CAUSES OF EXERCISE INDUCED ARTERIAL HYPOXEMIA

Although a significant amount of research is being conducted in an attempt to elucidate the mechanism underlying exercise induced arterial hypoxemia (7, 11, 20, 23, 24, 26, 39-43, 49), the causes of exercise induced arterial hypoxemia are not clearly understood and remain a topic of debate. A number of mechanisms have been identified

as likely contributors to the development of exercise induced arterial hypoxemia however their relative importance is currently unknown.

Ventilation-Perfusion Heterogeneity and Veno-Arterial Shunt

The distribution of alveolar ventilation ($\dot{V}_A$) and pulmonary capillary perfusion ($\dot{Q}_C$) or $\dot{V}_A$:$\dot{Q}_C$ throughout the lung is not uniform and actually becomes less uniform during heavy exercise (49). This $\dot{V}_A$:$\dot{Q}_C$ heterogeneity, accompanied by a left to right heart shunt, explains most of the widening (2.5- to 3-fold) of the alveolar to arterial PO_2 difference ((A-a)DO_2) in healthy, sedentary individuals (9). It should be noted that although there is a widening of the (A-a)DO_2 in healthy, sedentary individuals, they maintain their P_aO_2 to within roughly 10 mmHg of resting values and therefore do not exhibit exercise induced arterial hypoxemia.

Diffusion disequilibrium

Abnormal widening of the (A-a)DO_2 or diffusion disequilibrium has been suggested to be the other major cause of exercise induced arterial hypoxemia (15, 26, 42, 43, 49). The additional widening of the (A-a)DO_2 beyond that seen in healthy, sedentary individuals is thought to be due to a decrease in red blood cell transit time below the level necessary for full equilibration of pulmonary blood with alveolar gas or a decrease in the diffusing capacity of the pulmonary system (12, 42, 49). The cause of this reduced transit time is an increase in pulmonary blood flow beyond the point at which pulmonary capillary blood volume has reached its maximum morphological limits (9, 19). An increased diffusion distance, due to extremely high pulmonary capillary pressures and increased plasma leakage into the interstitial spaces referred to as pulmonary edema, may also contribute further to the widening (A-a)DO_2 due to (7, 9, 49).

Relative Hypoventilation

Inadequate hyperventilation has been suggested as one of the major causes of exercise induced arterial hypoxemia in highly trained endurance athletes. The lack of an appropriate hyperventilatory response to exercise causes an increased widening of the (A-a)DO_2 resulting in a drop in P_aO_2 (9, 49).

Mechanical limitation of ventilation and respiratory muscle fatigue

The difference in maximal exercise ventilation corrected for metabolic rate between healthy, untrained individuals ($\dot{V}_E/\dot{V}_{O_2} = 19.0 \pm 0.4$, $\dot{V}_E/\dot{V}_{CO_2} = 22.6 \pm 0.7$) and highly trained endurance athletes ($\dot{V}_E/\dot{V}_{O_2} = 15.7 \pm 0.2$, $\dot{V}_E/\dot{V}_{CO_2} = 19.0 \pm 0.7$) at low exercise intensities suggests that mechanical limitation of ventilation or respiratory muscle fatigue might explain, at least in part, the lack of an appropriate hyperventilatory response in athletes who develop exercise induced arterial hypoxemia (30). The hypothesis regarding mechanical limitation of ventilation is supported by experiments in which the mechanical work of breathing was reduced in subjects breathing a mixture of helium (He) and O_2 which resulted in an immediate and significant hyperventilation (11) as well as the observation that maximal volitional expiratory flow:volume limits may be exceeded at very high levels of exercise (14).

Whatever the relative contributions of these mechanisms to the development of exercise induced arterial hypoxemia in the highly trained, endurance athlete, it seems clear that factors influencing the control of the ventilatory response to exercise must also be considered as playing a role in the development of exercise induced arterial hypoxemia.

VENTILATORY CONTROL

Despite abundant scientific inquiry, the topic of ventilatory control is not fully understood and remains controversial. Until recently (20), ventilatory control has not been directly studied as a potential contributing factor in exercise induced arterial hypoxemia although a number of investigations of exercise induced arterial hypoxemia have included a description of the ventilatory response accompanying the exercise stimulus .

CONTROL MECHANISMS

The current body of data has led some researchers (48) to hypothesize a system of ventilatory regulation during exercise based upon the fact that in normal individuals, exercising at moderate intensities (ranging from rest to the anaerobic threshold) P_aCO_2, pH and PO_2 are regulated at essentially their resting values. One hypothesized structure for the ventilatory controller combines feed-forward and feed-back mechanisms (48). The actual physiological mechanisms that could contribute to the feed-forward response are summarized below:

1. arterial CO_2 (pH) oscillations sensed by the carotid body,
2. central neural stimulus to the respiratory center from the motor cortex,
3. afferent input from exercising muscles to the respiratory center,
4. venous return to the heart sensed by some unknown mechanism,
5. a sensor responding to pulmonary blood flow, mixed venous CO_2, CO_2 flux to the lung, or some other unknown humoral substance,
6. an intrapulmonary chemoreceptor, also not yet identified, sensing mixed venous blood pH.

This feed-forward response would yield an exercise ventilation proportional to the CO_2 production, with any errors in this feed-forward response being corrected by the feed-back response of the arterial chemoreceptors to P_aCO_2 (48).

CENTRAL CONTROL OF VENTILATION

The central nervous system plays an important role in the regulation of the ventilatory response to exercise. The regulation is accomplished through the integration of sensory input via three basic types of mechanisms; non-chemical input from supra-pontine areas of the brain, chemical input from chemoreceptive regions of the medulla, and spinal motor neuron cross innervation (13).

Supra-pontine Control

The supra-pontine portion of the ventilatory control equation, plays an important role in the ventilatory response of humans during exercise. Its effect is obtained through the integration of three basic influences. The traditional voluntary influence of the higher centers has obvious and significant application to the control of breathing in athletic endeavors where the ventilatory musculature in also involved in the activity directly (13). The second influence of the higher centers is effected through the sensation of ventilatory effort. A number of receptors including, but not limited to, pulmonary and airway stretch receptors, intercostal muscle spindles, and costo-vertebral joint receptors are located in such a way that they provide feedback to the motor cortex regarding lung volume, rib cage distortion, upper airway resistance, development of muscle tension, and other important determinants of ventilatory sensation (13). The third category of contributions from higher levels of the CNS involves more direct influences of supra-pontine mechanisms on medullary output and the interaction of these inputs with the more

traditional chemoreceptor inputs to the same areas. These mechanisms are generally classified into two groups, cortical inputs (inhibitory) and diencephalic inputs (facilatory) however the activation of these influences is not clearly understood (13).

Central Chemoreception

The majority of the resting ventilatory response of normal individuals at sea level is mediated by the central chemoreceptors. Medullary chemoreceptive cells on the ventral surface of the medulla are sensitive to changes in the pH of the medullary interstitial fluid and cerebrospinal fluid with decreases in pH stimulating ventilation (2). Due to the presence of the blood-brain barrier, which is more permeable to CO_2 than to H^+ ions, these receptors are not influenced by arterial pH but rather by P_aCO_2. These receptors are responsible for maintaining a ventilatory response adequate to maintain a resting P_aCO_2 of about 40 to 45 mmHg.

Spinal Motor Neuron Interaction

The influence of the spinal motor neurons on the control of ventilation is not clearly understood. The motor neurons do not generate rhythmic discharge but do show reciprocal inhibition. They receive input from a variety of sources including mechanoreceptor afferents, phasic command signals and tonic decending influences. They could, in combination with the above mentioned mechanisms, conceivably generate an appropriate ventilatory response to exercise without inputs arising from outside the central nervous system (13).

PERIPHERAL CONTROL OF VENTILATION

Peripheral influences on the ventilatory response to exercise come from primarily two sources, peripheral mechanoreceptors and peripheral chemoreceptors. The integration

of afferent signals from these receptors with others mentioned previously allow the close regulation of P_aO_2, P_aCO_2 and pH_a observed in normal individuals at sea level.

Peripheral Mechanoreceptors

A number of receptors have been identified that could play a role in the regulation of the ventilatory response to exercise. These receptors, some of which are skeletal muscle spindles, Golgi tendon organs, and skeletal joint proprioceptors, send afferent signals to the sensory cortex (2) and are thought to play a significant role in the neurogenic or phase 1 portion of the ventilatory response to exercise (55).

Peripheral Chemoreceptors

Peripheral chemoreceptors are of basically two types, aortic body chemoreceptors and carotid body chemoreceptors. Both receptors respond to changes in blood gas tensions however their relative importance in the control of ventilation is quite different.

Aortic Body Chemoreceptors

The aortic bodies are located around the aortic arch and between the arch and the pulmonary artery and are therefore appropriately located to respond to changes in the chemical composition of arterial blood. They are stimulated by a decreased mean P_aO_2 and by an increased mean P_aCO_2, the response to O_2 being greater (34). Although the aortic body chemoreceptors are involved in respiratory regulation, the role of the carotid body chemoreceptors is much greater.

Carotid Body Chemoreceptors

The carotid body chemoreceptors are located in the carotid bodies which are found at the bifurcation of the common carotid arteries into the internal and external carotid arteries. Like the aortic bodies, they are stimulated by decreasing P_aO_2 and by increasing P_aCO_2, however they are also stimulated by a decrease in pH_a (34) and

increasing blood potassium ($[K^+]$) levels (38). In addition, the carotid bodies respond quickly enough to be sensitive to the within-breath variations of pH_a caused by within breath fluctuations in P_ACO_2, possibly providing one of the more important signals used to match ventilation to metabolic rate during exercise (34). That the carotid bodies play an important role in the control of exercise ventilation is clear (4, 17, 28, 36, 50). In addition, experiments involving 100% O_2 breathing during exercise have indicated that the maximal reduction in ventilation during administration of 100% O_2 (i.e., 'silencing' the carotid bodies) is greater during exercise than at rest suggesting enhancement of carotid body drive induced by exercise (55).

The importance of the chemoreceptive drive to breath is clear, playing a role in both the feed-forward and feed-back portions of the respiratory control mechanism, its briskness has profound effects on the ability to maintain homeostasis during moderate to intense exercise. Variations in carotid body drives have been suggested to play a role in the control of exercise ventilation. Carotid drives have been reported to increase (25) and decrease (35) significantly with training and during exercise compared to rest (21, 22, 51). For example, carotid body chemoresponsiveness to hypercapnia has been reported to range from 0.38 ± 0.14 $L \cdot min^{-1} \cdot mmHg^{-1}$ in healthy untrained individuals (32) to as high as 2.15 ± 0.62 $L \cdot min^{-1} \cdot mmHg^{-1}$ in highly trained endurance athletes at rest (25). Thus, individual differences in variations in carotid body drives during exercise could explain some of the variation in the ventilatory response to exercise and development of exercise induced arterial hypoxemia in highly trained endurance athletes.

APPENDIX B

TABLES

Table 6 Age, height, mass, and body surface area, individual subject data.

SUBJECT	AGE (yrs)	HEIGHT (cm)	MASS (kg)	BSA (m^2)
TM	28	177	65.7	1.81
PT	31	183	84.0	2.06
DB	27	190	76.3	2.03
GA	24	184	81.4	2.04
HT	24	174	69.8	1.84
BT	46	179	79.7	1.98
RR	28	184	78.6	2.01
SF	25	178	74.7	1.93
MF	33	184	79.9	2.03
DH	21	191	80.8	2.09
ME	20	189	80.8	2.08
JF	22	174	67.2	1.80
MEAN ± SD	27 ± 7	182 ± 6	76.6 ± 6.0	1.98 ± 0.11

Table 7 Pulmonary function, individual subject data.

SUBJECT	FVC (L) (% Pred.)	FEV_1 (L) (% Pred.)	FEV_1/FVC	FEF_{max} ($L \cdot sec^{-1}$) (% Pred.)	MVV ($L \cdot min^{-1}$) (% Pred.)
TM	5.21 98	3.72 84	0.71	9.40 114	183 105
PT	6.99 122	4.80 101	0.69	11.58 133	211 115
DB	6.31 98	5.39 101	0.85	12.07 138	203 102
GA	5.71 95	5.27 105	0.92	13.48 152	221 114
HT	6.20 120	4.25 98	0.69	9.70 116	183 102
BT	5.13 104	3.99 99	0.78	11.90 146	203 128
RR	6.39 107	4.62 94	0.72	8.10 93	184 97
SF	6.18 112	4.07 88	0.66	9.18 107	158 85
MF	5.91 102	4.91 102	0.83	9.25 107	192 105
DH	7.31 109	5.74 103	0.79	11.36 125	231 111
ME	7.20 107	5.40 98	0.75	9.55 105	177 86
JF	4.77 92	4.15 95	0.87	10.65 128	178 98
MEAN ± SD	6.11 ± 0.82 105 ± 9	4.69 ± 0.66 97 ± 6	0.77 ± 0.08	10.52 ± 1.57 122 ± 18	194 ± 21 97 ± 11

Table 8 $\dot{V}_{O_2max}$, peak power output, and S_aO_2max, individual subject data.

SUBJECT	$\dot{V}_{O_2max}$ ($L \cdot min^{-1}$)	$\dot{V}_{O_2max}$ ($mL \cdot min^{-1} \cdot kg^{-1}$)	Peak Power (Watts)	S_aO_2max (%)
TM	4.92	74.9	470	90.0
PT	5.25	62.5	490	90.4
DB	5.21	68.3	479	90.0
GA	4.85	59.6	430	91.0
HT	5.14	73.6	470	89.6
BT	4.88	61.5	465	90.2
RR	5.15	65.5	435	93.4
SF	4.88	65.3	435	93.3
MF	5.00	62.6	455	93.2
DH	5.65	69.9	450	94.2
ME	5.54	68.6	490	93.1
JF	4.50	67.0	400	88.0
MEAN ± SD	5.08 ± 0.32	66.6 ± 4.7	456 ± 27	91.4 ± 2.0

S_aO_2max is the lowest arterial hemoglobin saturation during maximal cycle ergometer test.

Table 9 $\dot{V}_{O_2TH}$, and power output at $\dot{V}_{O_2TH}$, individual data.

SUBJECT	$\dot{V}_{O_2TH}$ ($L \cdot min^{-1}$)	$\dot{V}_{O_2TH}$ ($mL \cdot min^{-1} \cdot kg^{-1}$)	Power at $\dot{V}_{O_2TH}$ (Watts)
TM	3.22	49.9	300
PT	3.34	43.8	330
DB	3.36	45.6	310
GA	3.11	41.2	275
HT	3.48	53.0	335
BT	3.10	40.2	280
RR	3.41	43.4	265
SF	3.27	43.8	256
MF	3.15	39.4	258
DH	3.40	42.1	246
ME	3.34	41.3	270
JF	3.24	48.2	270
MEAN ± SD	3.29 ± 0.12	44.3 ± 4.2	283 ± 29

Table 10 Workloads during chemoresponse tests, individual subject data.

	Exercise Level		
GROUP	VLPO	LPO	MPO
TM	70	190	260
PT	80	220	280
DB	60	180	310
GA	70	180	260
HT	90	220	300
BT	60	200	270
RR	60	200	230
SF	80	200	230
MF	70	190	220
DH	80	190	230
ME	95	215	250
JF	60	170	225
MEAN ± SD	73 ± 12	196 ± 16	255 ± 30

Values are means ± SD. Units are Watts; LOS, low oxygen saturation; NOS, normal oxygen saturation. VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Table 11 Hypercapnic peripheral chemoresponse, individual subject data.

	Exercise Level			
SUBJECT	Rest	VLPO	LPO	MPO
TM	0.24 ± 0.19	0.86 ± 0.33	0.74 ± 0.19	0.76 ± 0.31
PT	0.41 ± 0.08	0.66 ± 0.20	1.06 ± 0.26	0.99 ± 0.23
DB	0.60 ± 0.27	0.93 ± 0.37	1.14 ± 0.38	0.54 ± 0.11
GA	0.49 ± 0.26	0.73 ± 0.15	0.87 ± 0.38	0.80 ± 0.20
HT	0.22 ± 0.10	0.44 ± 0.27	0.64 ± 0.18	0.77 ± 0.29
BT	1.13 ± 0.29	0.65 ± 0.21	0.67 ± 0.25	0.86 ± 0.31
RR	0.60 ± 0.22	1.43 ± 0.53	1.75 ± 0.38	1.64 ± 0.38
SF	0.68 ± 0.17	0.87 ± 0.16	0.69 ± 0.26	0.98 ± 0.32
MF	0.99 ± 0.47	1.45 ± 0.61	1.13 ± 0.23	1.20 ± 0.33
DH	0.54 ± 0.30	1.05 ± 0.49	1.57 ± 0.45	1.59 ± 0.79
ME	0.37 ± 0.31	1.16 ± 0.66	1.24 ± 0.33	0.72 ± 0.50
JF	0.16 ± 0.20	0.53 ± 0.19	1.00 ± 0.40	1.17 ± 0.32
mean ± SD	0.54 ± 0.30	0.90 ± 0.33	1.04 ± 0.36	1.00 ± 0.34

Values are means ± SD Units are $L \cdot min^{-1} \cdot mmHg^{-1}$; LOS, low oxygen saturation; NOS, normal oxygen saturation. VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Table 12 Hypercapnic peripheral chemoresponse, group data.

	Exercise Level			
GROUP	Rest	VLPO	LPO	MPO
LOS (n=7)	0.46 ± 0.33	0.69 ± 0.17	0.87 ± 0.20	0.84 ± 0.20
NOS (n=5)	0.64 ± 0.23	1.19 ± 0.25	1.28 ± 0.41	1.23 ± 0.39

Values are means ± SD. Units are $L \cdot min^{-1} \cdot mmHg^{-1}$; LOS, low oxygen saturation; NOS, normal oxygen saturation. VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Table 13 Pre-hypercapnic peripheral chemoresponse S_aO_2, individual subject data.

	Exercise Level			
SUBJECT	Rest	VLPO	LPO	MPO
TM	98.8 ± 1.0	97.9 ± 0.5	97.1 ± 0.7	95.9 ± 0.6
PT	98.0 ± 0.0	97.8 ± 1.1	99.3 ± 0.7	95.9 ± 1.6
DB	97.7 ± 1.3	97.7 ± 0.7	96.0 ± 0.7	95.0 ± 0.6
GA	99.0 ± 0.8	96.7 ± 0.1	97.0 ± 0.9	94.7 ± 1.0
HT	97.0 ± 0.6	96.0 ± 0.6	96.6 ± 0.7	95.6 ± 0.9
BT	96.6 ± 0.8	97.7 ± 0.7	96.6 ± 0.5	96.0 ± 0.8
RR	99.1 ± 0.9	97.4 ± 0.9	97.2 ± 0.8	96.3 ± 1.7
SF	96.7 ± 1.0	97.3 ± 0.9	96.2 ± 1.9	96.2 ± 0.9
MF	96.5 ± 0.5	97.0 ± 0.8	96.0 ± 0.8	96.3 ± 1.4
DH	98.4 ± 0.9	97.3 ± 0.5	96.2 ± 0.7	96.4 ± 1.0
ME	96.8 ± 0.8	96.5 ± 0.5	95.4 ± 1.0	96.1 ± 0.6
JF	96.9 ± 1.3	97.6 ± 1.3	96.0 ± 1.6	93.6 ± 1.6
MEAN ± SD	97.6 ± 1.0	97.2 ± 0.6	96.6 ± 1.0	95.7 ± 0.8

Values are means ± SD. Units are %. VLPO, very low power output; LPO, low power output; MPO, moderate power output. saturation. VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Table 14 Pre-hypercapnic peripheral chemoresponse S_aO_2, group data.

	Exercise Level			
GROUP	Rest	VLPO	LPO	MPO
LOS (n=7)	97.7 ± 0.9	97.4 ± 0.7	96.9 ± 1.1	95.2 ± 0.9
NOS (n=5)	97.5 ± 1.2	97.1 ± 0.4	96.2 ± 0.7	96.3 ± 0.1

Values are means ± SD. Units are %; LOS, low oxygen saturation; NOS, normal oxygen saturation. VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Table 15 Hyperoxic peripheral chemoresponse, group data.

	Exercise Level			
GROUP	Rest	VLPO	LPO	MPO
LOS (n=7)	18.6 ± 8.8	19.1 ± 6.8	16.2 ± 4.0	17.1 ± 5.2
NOS (n=5)	22.1 ± 7.5	15.9 ± 6.5	16.2 ± 5.5	17.7 ± 5.5

Values are means ± SD. Units are %; LOS, low oxygen saturation; NOS, normal oxygen saturation. VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Table 16 Hyperoxic peripheral chemoresponse, individual subject data.

	Exercise Level			
SUBJECT	Rest	VLPO	LPO	MPO
TM	11.0	16.4	11.5	17.5
PT	28.8	25.2	19.4	26.0
DB	12.4	9.2	11.4	16.3
GA	9.2	11.3	13.5	10.7
HT	16.7	24.7	20.6	12.5
BT	31.5	24.0	17.4	15.2
RR	21.8	8.2	12.0	7.3
SF	25.0	25.5	19.0	17.2
MF	9.8	13.3	8.8	17.2
DH	29.9	18.7	21.7	21.7
ME	24.0	14.0	19.3	19.3
JF	20.3	23.0	19.6	21.2
MEAN ± SD	20.0 ± 8.1	17.8 ± 6.6	16.2 ± 4.4	16.8 ± 5.1

Units are %. VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Table 17 Pre-hyperoxic peripheral chemoresponse S_aO_2, group data.

	Exercise Level			
GROUP	Rest	VLPO	LPO	MPO
LOS (n=7)	97.7 ± 0.9	97.3 ± 0.5	96.1 ± 0.8	95.6 ± 1.1
NOS (n=5)	97.8 ± 0.8	97.6 ± 0.7	96.4 ± 0.6	96.3 ± 0.8

Values are means ± SD. Units are %; LOS, low oxygen saturation; NOS, normal oxygen saturation. VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Table 18 Pre-hyperoxic peripheral chemoresponse S_aO_2, individual subject data.

	Exercise Level			
SUBJECT	Rest	VLPO	LPO	MPO
TM	99.4 ± 1.4	98.1 ± 1.0	97.2 ± 0.5	97.2 ± 0.9
PT	97.0 ± 1.1	96.8 ± 0.8	96.1 ± 0.8	96.2 ± 1.0
DB	97.6 ± 0.6	96.7 ± 0.9	95.4 ± 1.1	95.0 ± 0.7
GA	98.0 ± 0.8	97.9 ± 0.4	96.5 ± 0.4	96.2 ± 0.6
HT	97.0 ± 1.3	97.2 ± 0.9	97.0 ± 0.6	96.3 ± 0.7
BT	96.7 ± 2.1	97.2 ± 0.8	95.8 ± 0.9	94.3 ± 1.4
RR	97.2 ± 1.3	98.2 ± 1.3	96.1 ± 1.3	96.1 ± 1.3
SF	96.9 ± 1.1	97.2 ± 1.0	96.1 ± 1.1	96.0 ± 0.5
MF	97.9 ± 1.7	98.1 ± 0.9	97.5 ± 1.2	95.4 ± 1.7
DH	97.9 ± 0.9	96.5 ± 0.6	96.3 ± 0.9	97.5 ± 0.5
ME	98.9 ± 1.9	97.8 ± 0.5	96.2 ± 0.8	96.6 ± 1.0
JF	98.3 ± 1.2	96.9 ± 1.2	94.9 ± 1.6	94.2 ± 1.0
MEAN ± SD	97.7 ± 0.8	97.4 ± 0.6	96.3 ± 0.7	95.9 ± 1.0

Values are means ± SD. Units are %. VLPO, very low power output; LPO, low power output; MPO, moderate power output. saturation. VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Table 19 RMANOVA, Hypercapnic Chemoresponse.

UNIVARIATE AND MULTIVARIATE REPEATED MEASURES ANALYSIS							
BETWEEN SUBJECTS							
SOURCE	SS	DF	MS	F	P		
GROUP	1.563	1	1.563	13.652	0.004		
ERROR	1.145	10	0.115				
WITHIN SUBJECTS							
SOURCE	SS	DF	MS	F	P	G-G	H-F
LEVELS	2.012	3	0.671	10.446	0.000	0.001	0.000
LEVELS X GROUPS	0.172	3	0.057	0.894	0.456	0.426	0.451
ERROR	1.926	30	0.064				
				GREENHOUSE-GEISSER EPSILON:		0.6811	
				HUYNH-FELDT EPSILON:		0.9433	

Table 20 Polynomial Contrasts, Hypercapnic Chemoresponse.

SINGLE DEGREE OF FREEDOM POLYNOMIAL CONTRASTS					
POLYNOMIAL TEST OF ORDER 1 (LINEAR)					
SOURCE	SS	DF	MS	F	P
LEVELS	1.469	1	1.469	13.413	0.004
LEVELS X GROUPS	0.042	1	0.042	0.380	0.552
ERROR	1.095	10	0.110		
POLYNOMIAL TEST OF ORDER 2 (QUADRATIC)					
SOURCE	SS	DF	MS	F	P
LEVELS	0.540	1	0.540	8.197	0.017
LEVELS X GROUPS	0.090	1	0.090	1.370	0.269
ERROR	0.658	10	0.066		
POLYNOMIAL TEST OF ORDER 3 (CUBIC)					
SOURCE	SS	DF	MS	F	P
LEVELS	0.003	1	0.003	0.189	0.673
LEVELS X GROUPS	0.040	1	0.040	2.343	0.157
ERROR	0.173	10	0.017		

Table 21 RMANOVA, Pre-Hypercapnic Chemoresponse S_aO_2.

UNIVARIATE AND MULTIVARIATE REPEATED MEASURES ANALYSIS							
BETWEEN SUBJECTS							
SOURCE	SS	DF	MS	F	P		
GROUP	0.024	1	0.024	0.019	0.894		
ERROR	13.092	10	1.309				
WITHIN SUBJECTS							
SOURCE	SS	DF	MS	F	P	G-G	H-F
LEVELS	23.103	3	7.701	15.120	0.000	0.000	0.000
LEVELS X GROUPS	4.909	3	1.636	3.213	0.037	0.044	0.037
ERROR	15.280	30	0.509				
GREENHOUSE-GEISSER EPSILON: 0.8860							
HUYNH-FELDT EPSILON: 1.0000							

Table 22 Polynomial Contrasts, Pre-Hypercapnic Chemoresponse S_aO_2.

SINGLE DEGREE OF FREEDOM POLYNOMIAL CONTRASTS					
POLYNOMIAL TEST OF ORDER 1 (LINEAR)					
SOURCE	SS	DF	MS	F	P
LEVELS	22.548	1	22.548	34.299	0.000
LEVELS X GROUPS	1.488	1	1.488	2.264	0.163
ERROR	6.574	10	0.657		
POLYNOMIAL TEST OF ORDER 2 (QUADRATIC)					
SOURCE	SS	DF	MS	F	P
LEVELS	0.550	1	0.550	1.555	0.241
LEVELS X GROUPS	2.333	1	2.333	6.596	0.028
ERROR	3.537	10	0.354		
POLYNOMIAL TEST OF ORDER 3 (CUBIC)					
SOURCE	SS	DF	MS	F	P
LEVELS	0.005	1	0.005	0.010	0.922
LEVELS X GROUPS	1.088	1	1.088	2.105	0.177
ERROR	5.169	10	0.517		

Table 23 RMANOVA, Hyperoxic Chemoresponse.

UNIVARIATE AND MULTIVARIATE REPEATED MEASURES ANALYSIS							
BETWEEN SUBJECTS							
SOURCE	SS	DF	MS	F	P		
GROUP	0.026	1	0.026	0.000	0.988		
ERROR	1081.887	10	108.189				
WITHIN SUBJECTS							
SOURCE	SS	DF	MS	F	P	G-G	H-F
LEVELS	117.389	3	39.130	2.152	0.115	0.130	0.115
LEVELS X GROUPS	66.757	3	22.252	1.224	0.318	0.317	0.318
ERROR	545.572	30	18.186				
GREENHOUSE-GEISSER EPSILON:						0.8019	
HUYNH-FELDT EPSILON:						1.0000	

Table 24 Polynomial Contrasts, Hyperoxic Chemoresponse.

SINGLE DEGREE OF FREEDOM POLYNOMIAL CONTRASTS					
POLYNOMIAL TEST OF ORDER 1 (LINEAR)					
SOURCE	SS	DF	MS	F	P
LEVELS	83.122	1	83.122	2.968	0.116
LEVELS X GROUPS	11.933	1	11.933	0.426	0.529
ERROR	280.023	10	28.002		
POLYNOMIAL TEST OF ORDER 2 (QUADRATIC)					
SOURCE	SS	DF	MS	F	P
LEVELS	34.114	1	34.114	2.267	0.163
LEVELS X GROUPS	28.392	1	28.392	1.887	0.200
ERROR	150.498	10	15.050		
POLYNOMIAL TEST OF ORDER 3 (CUBIC)					
SOURCE	SS	DF	MS	F	P
LEVELS	0.153	1	0.153	0.013	0.911
LEVELS X GROUPS	26.432	1	26.432	2.297	0.161
ERROR	115.051	10	11.505		

Table 25 RMANOVA, Pre-Hyperoxic Chemoresponse S_aO_2.

UNIVARIATE AND MULTIVARIATE REPEATED MEASURES ANALYSIS							
BETWEEN SUBJECTS							
SOURCE	SS	DF	MS	F	P		
GROUP	1.332	1	1.332	0.966	0.349		
ERROR	13.791	10	1.379				
WITHIN SUBJECTS							
SOURCE	SS	DF	MS	F	P	G-G	H-F
LEVELS	25.502	3	8.501	18.769	0.000	0.000	0.000
LEVELS X GROUPS	0.619	3	0.206	0.456	0.715	0.669	0.715
ERROR	13.588	30	0.453				
GREENHOUSE-GEISSER EPSILON:						0.7780	
HUYNH-FELDT EPSILON:						1.0000	

Table 26 Polynomial Contrasts, Pre-Hyperoxic Chemoresponse S_aO_2.

SINGLE DEGREE OF FREEDOM POLYNOMIAL CONTRASTS					
POLYNOMIAL TEST OF ORDER 1 (LINEAR)					
SOURCE	SS	DF	MS	F	P
LEVELS	23.989	1	23.989	36.276	0.000
LEVELS X GROUPS	0.552	1	0.552	0.835	0.382
ERROR	6.613	10	0.661		
POLYNOMIAL TEST OF ORDER 2 (QUADRATIC)					
SOURCE	SS	DF	MS	F	P
LEVELS	0.001	1	0.001	0.002	0.967
LEVELS X GROUPS	0.011	1	0.011	0.019	0.892
ERROR	5.696	10	0.570		
POLYNOMIAL TEST OF ORDER 3 (CUBIC)					
SOURCE	SS	DF	MS	F	P
LEVELS	1.512	1	1.512	11.828	0.006
LEVELS X GROUPS	0.056	1	0.056	0.439	0.523
ERROR	1.278	10	0.128		

Table 27 Linear Regression, Hypercapnic Chemoresponse and Pre-Hypercapnic Chemoresponse S_aO_2, NOS subjects.

DEPENDANT VARIABLE IS SATURATION				
N	R	R^2	ADJ. R^2	S.E.E.
20	0.312	0.097	0.047	0.835

REGRESSION COEFFICIENTS						
VARIABLE	COEFF.	STD ERROR	STD COEF	TOLERANCE	T	P(2 TAIL)
CONSTANT	97.479	0.546	0.000	.	178.460	0.000
RESP	-0.660	0.474	-0.312	1.000	-1.392	0.181

ANALYSIS OF VARIANCE					
SOURCE	SS	DF	MS	F	P
REGRESSION	1.351	1	1.351	1.937	0.181
RESIDUAL	12.554	18	0.697		

Table 28 Linear Regression, Hypercapnic Chemoresponse and Pre-Hypercapnic Chemoresponse S_aO_2, LOS subjects.

DEPENDANT VARIABLE IS SATURATION				
N	R	R^2	ADJ. R^2	S.E.E.
28	0.338	0.115	0.080	1.247

REGRESSION COEFFICIENTS						
VARIABLE	COEFF.	STD ERROR	STD COEF	TOLERANCE	T	P(2 TAIL)
CONSTANT	97.954	0.666	0.000	.	146.979	0.000
RESP	-1.596	0.870	-0.338	1.000	-1.834	0.078

ANALYSIS OF VARIANCE					
SOURCE	SS	DF	MS	F	P
REGRESSION	5.227	1	5.227	3.364	0.078
RESIDUAL	40.400	26	1.554		

Table 29 Linear Regression, Hyperoxic Chemoresponse and Pre-Hyperoxic Chemoresponse S_aO_2, NOS subjects.

DEPENDANT VARIABLE IS SATURATION				
N	R	R^2	ADJ. R^2	S.E.E.
20	0.217	0.047	0.000	0.938

REGRESSION COEFFICIENTS						
VARIABLE	COEFF.	STD ERROR	STD COEF	TOLERANCE	T	P(2 TAIL)
CONSTANT	96.454	0.635	0.000	.	151.785	0.000
RESP	0.032	0.034	0.217	1.000	0.944	0.358

ANALYSIS OF VARIANCE					
SOURCE	SS	DF	MS	F	P
REGRESSION	0.784	1	0.784	0.890	0.358
RESIDUAL	15.848	18	0.880		

Table 30 Linear Regression, Hyperoxic Chemoresponse and Pre-Hyperoxic Chemoresponse S_aO_2, LOS subjects.

DEPENDANT VARIABLE IS SATURATION				
N	R	R^2	ADJ. R^2	S.E.E.
28	0.121	0.015	0.000	1.212

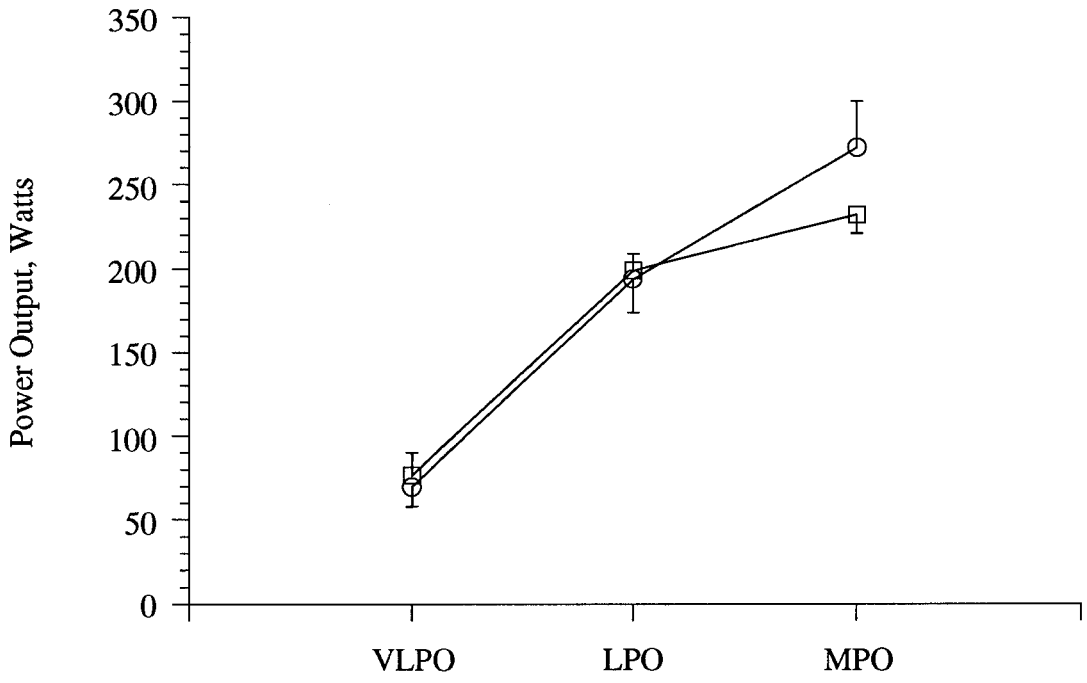
REGRESSION COEFFICIENTS						
VARIABLE	COEFF.	STD ERROR	STD COEF	TOLERANCE	T	P(2 TAIL)
CONSTANT	97.098	0.708	0.000	.	137.235	0.000
RESP	-0.023	0.038	-0.121	1.000	-0.621	0.540

ANALYSIS OF VARIANCE					
SOURCE	SS	DF	MS	F	P
REGRESSION	0.566	1	0.566	0.385	0.540
RESIDUAL	38.195	26	1.469		

APPENDIX C

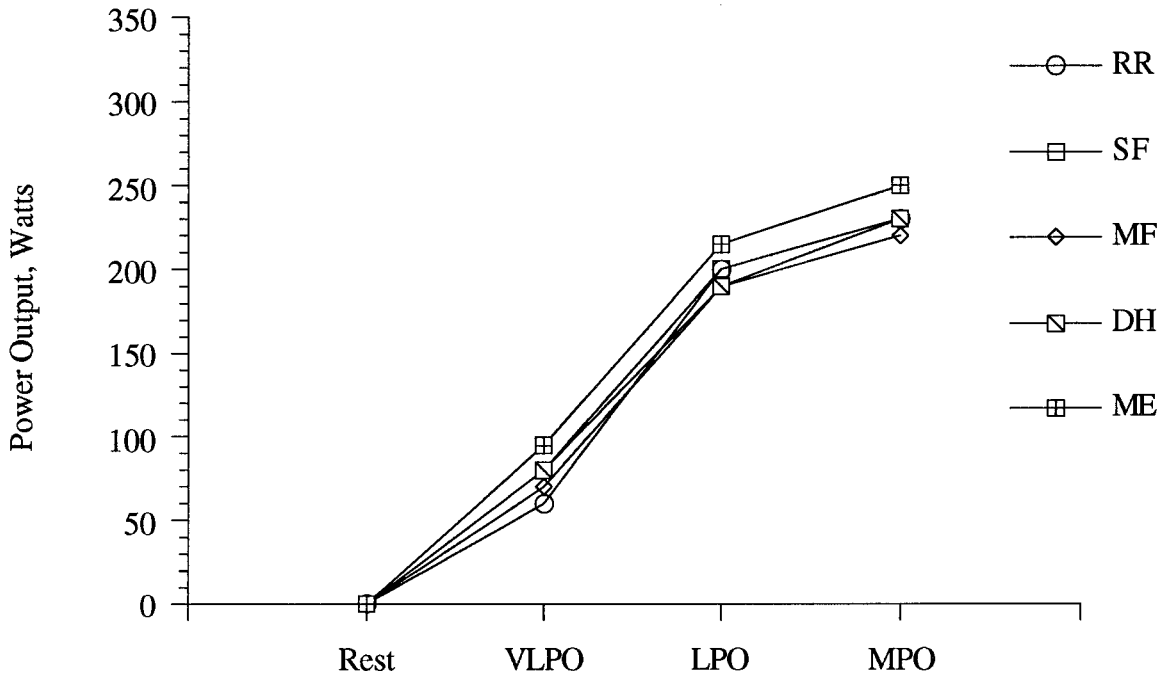
FIGURES

Figure 7 Power output at various exercise intensities, group data.



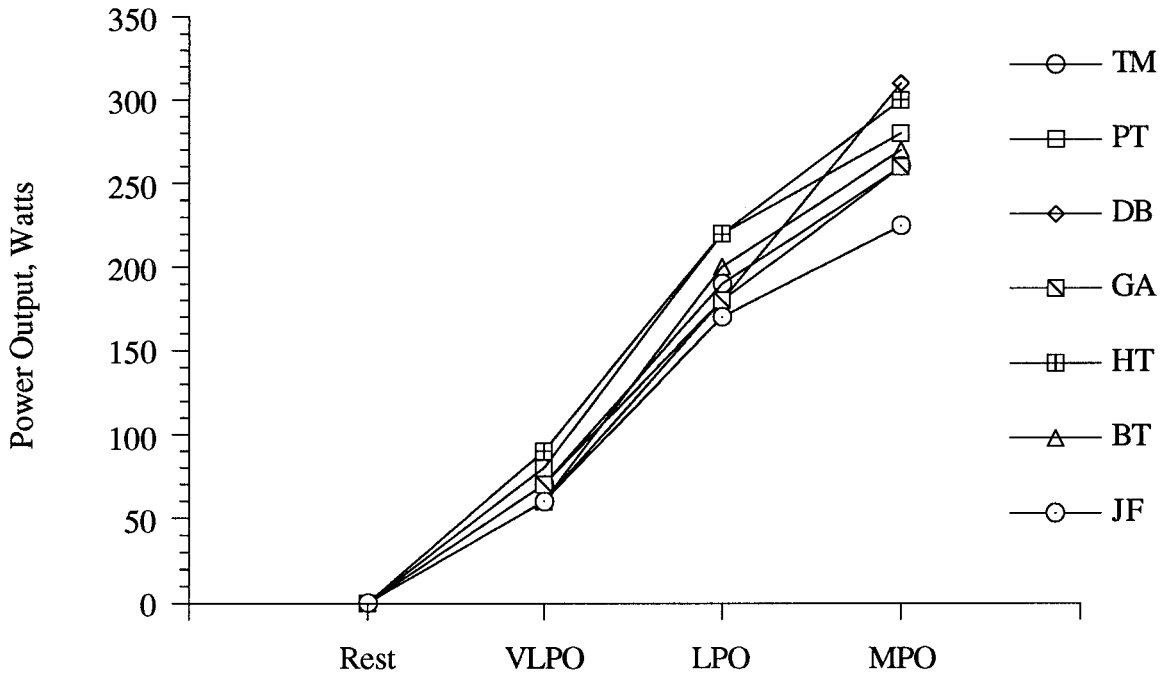
Values are means ± SD. Open circles, LOS, low oxygen saturation; Open squares, NOS, normal oxygen saturation. VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Figure 8 Power output at various exercise intensities, NOS subjects.



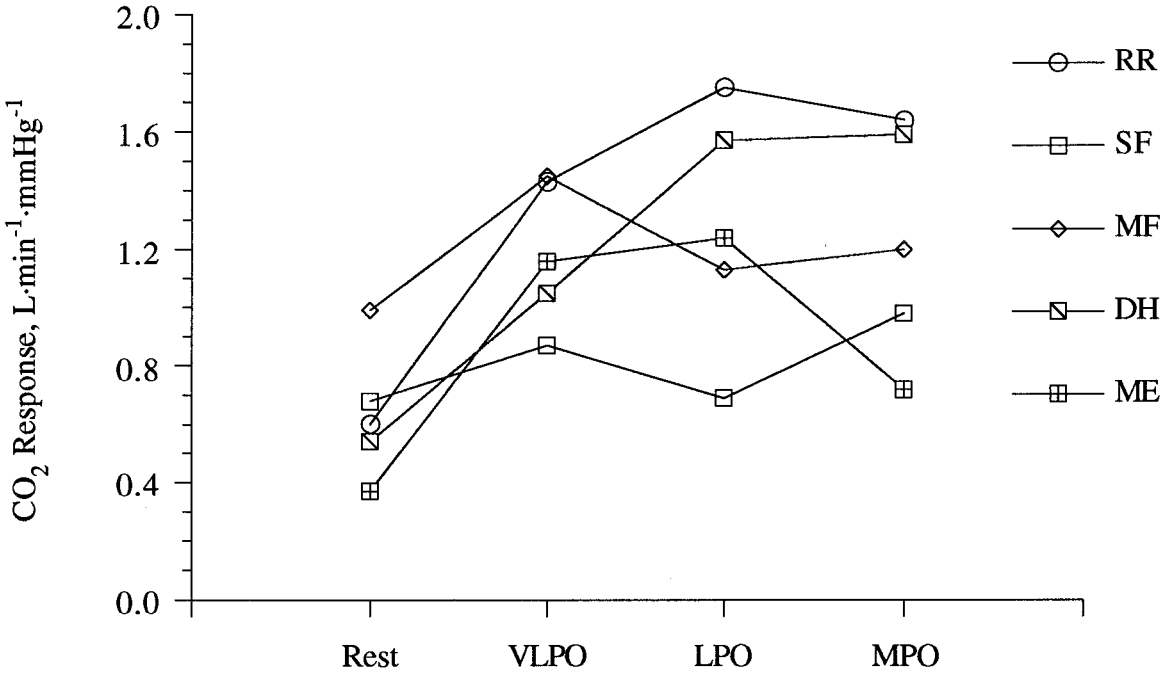
VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Figure 9 Power output at various exercise intensities, LOS subjects.



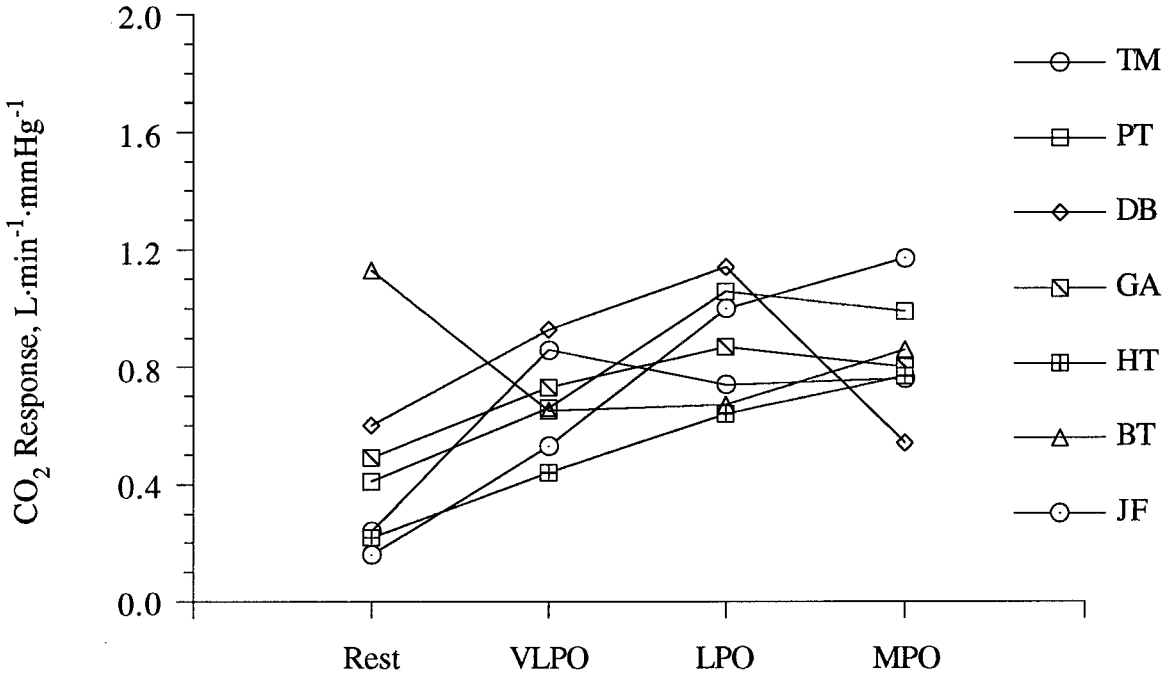
VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Figure 10 Hypercapnic peripheral chemoresponse at various exercise intensities, NOS subjects.



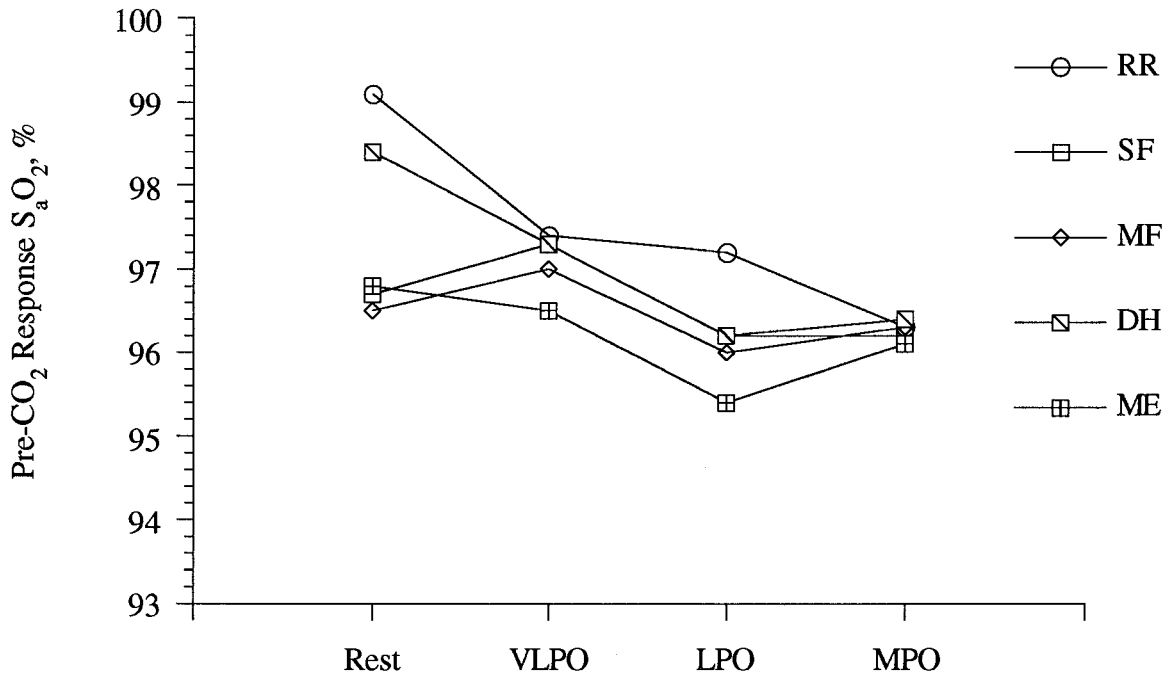
VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Figure 11 Hypercapnic peripheral chemoresponse at various exercise intensities, LOS subjects.



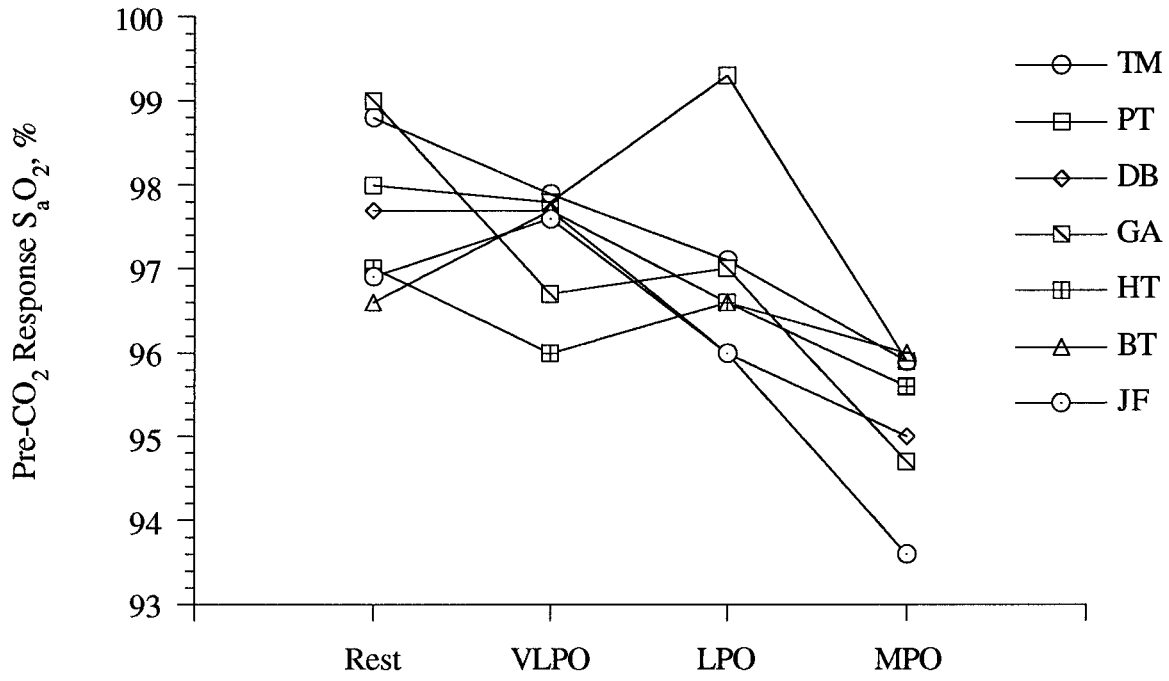
VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Figure 12 Pre-CO_2 response S_aO_2 at various exercise intensities, NOS subjects.



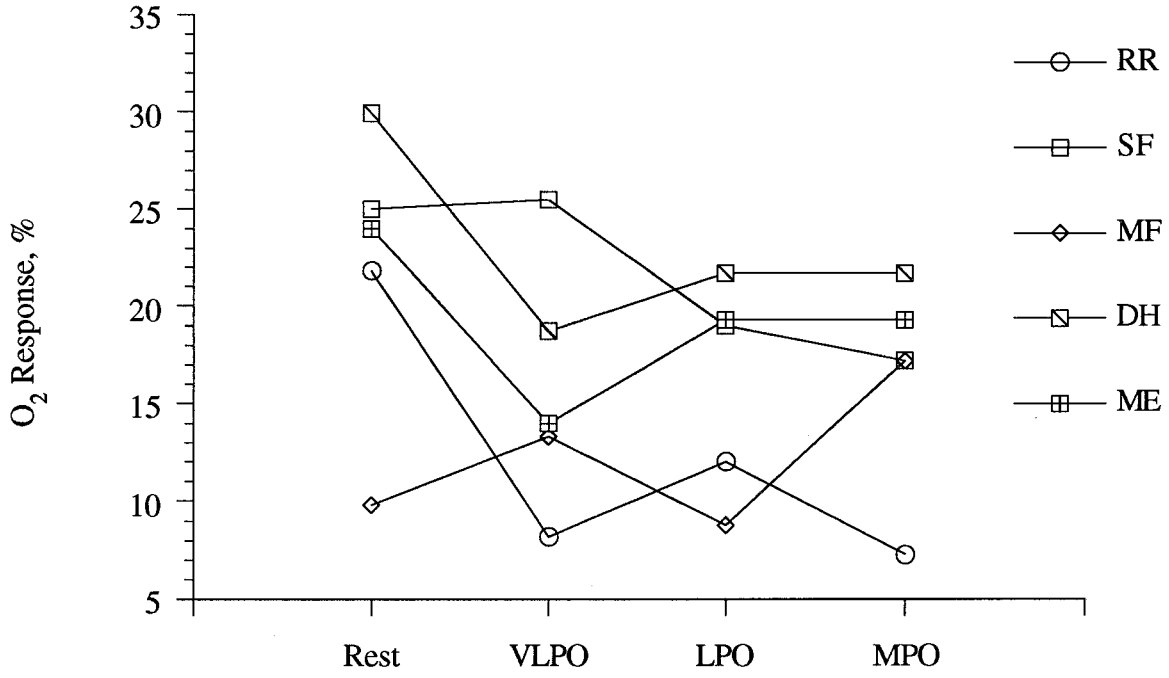
VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Figure 13 Pre-CO_2 response S_aO_2 at various exercise intensities, LOS subjects.



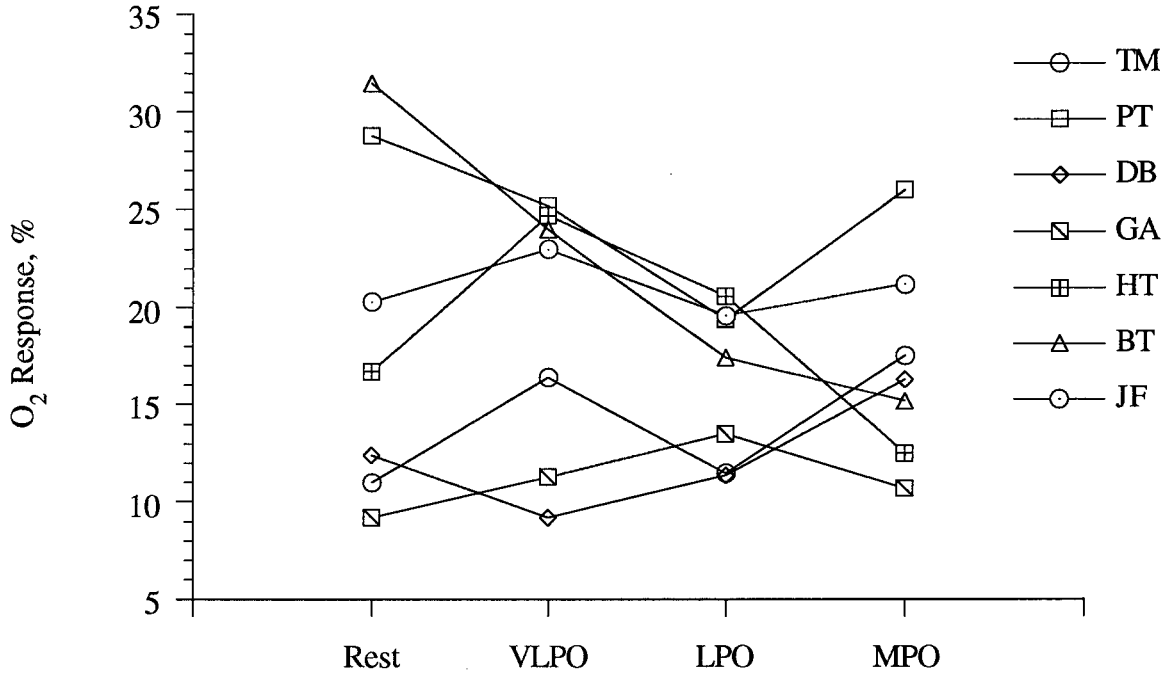
VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Figure 14 Hyperoxic peripheral chemoresponse at various exercise intensities, NOS subjects.



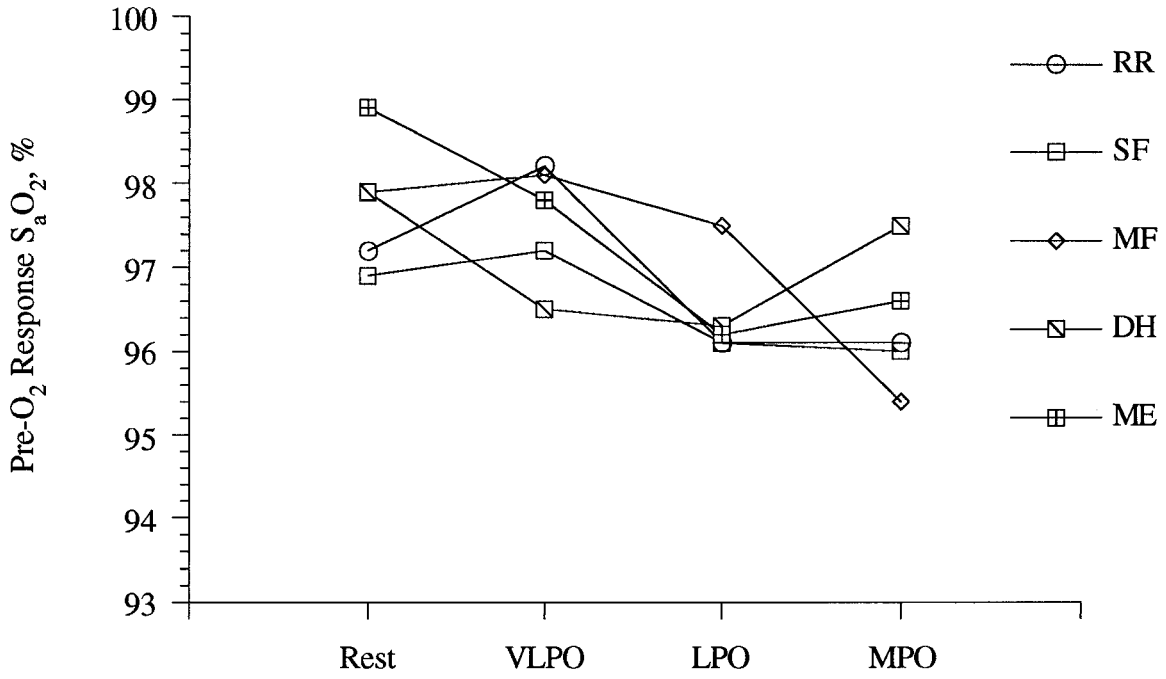
VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Figure 15 Hyperoxic peripheral chemoresponse at various exercise intensities, LOS subjects.



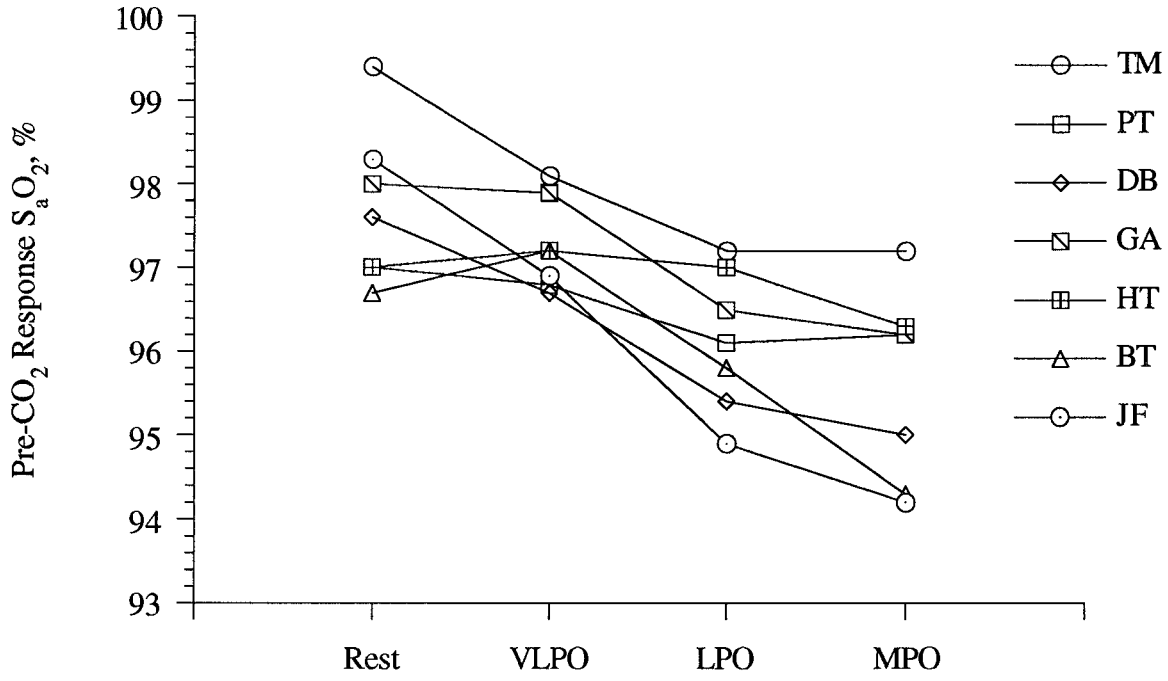
VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Figure 16 Pre-O_2 response S_aO_2 at various exercise intensities, NOS subjects.



VLPO, very low power output; LPO, low power output; MPO, moderate power output.

Figure 17 Pre-O_2 response S_aO_2 at various exercise intensities, LOS subjects.



VLPO, very low power output; LPO, low power output; MPO, moderate power output.

APPENDIX D

EXCLUDED SUBJECT DATA

Table 31 Age, height, mass, and body surface area, individual subject data.

Subject	Age (yrs)	Height (cm)	Mass (kg)	BSA (m^2)
AC	42	173	68.0	1.81
AS	21	180	73.4	1.93
BG	35	181	77.8	1.98
CA	27	181	77.2	1.97
CJ	26	172	61.0	1.72
DL	32	191	94.6	2.25
FH	35	176	68.3	1.83
FM	25	181	77.6	1.98
JG	34	191	94.0	2.23
JV	23	181	78.6	1.99
KR	25	187	88.2	2.14
MF-W	22	181	65.0	1.84
MF-J	23	178	68.1	1.85
MS	24	183	81.0	2.03
MT	25	180	70.2	1.89
MW	28	172	65.8	1.78
NG	28	180	77.6	1.97
PK	26	185	84.5	2.09
RH	25	186	80.7	2.06
RM	29	183	78.9	2.01
TC	27	185	85.3	2.10

TG	26	187	81.2	2.06
TR	37	193	92.0	2.23
TS	29	172	64.9	1.76
mean ± SD	28 ± 5	182 ± 6	77.2 ± 9.5	1.98 ± 0.15

Values are means ± SD.

Table 32 Age, height, mass, and body surface area, group data.

GROUP	Age (yrs)	Height (cm)	Mass (kg)	BSA (m^2)
UNFIT, NORMAL (n = 8)	30 ± 6	182 ± 7	79.7 ± 9.7	2.01 ± 0.16
UNFIT, EIH (n = 2)	29 ± 7	187 ± 6	87.5 ± 9.2	2.13 ± 0.14
FIT, NORMAL (n = 11)	28 ± 5	181 ± 6	75.5 ± 9.1	1.95 ± 0.15
FIT, EIH (n = 3)	24 ± 3	180 ± 2	70.1 ± 6.3	1.89 ± 0.07

Values are means ± SD. Groups are UNFIT, ($\dot{V}_{O_2max} < 5.00$ L·min^{-1} or 60.0 mL·min^{-1}·kg^{-1}); FIT, ($\dot{V}_{O_2max} \geq 5.00$ L·min^{-1} or 60.0 mL·min^{-1}·kg^{-1}); NORMAL, ($S_aO_{2max} >$ 91.0 %); EIH, ($S_aO_{2max} \leq 91.0$ %).

Table 33 $\dot{V}_{O_2max}$, peak power output, and lowest arterial hemoglobin saturation during maximal cycle ergometer test, individual subject data.

Subject	$\dot{V}_{O_2max}$ ($L \cdot min^{-1}$)	$\dot{V}_{O_2max}$ ($mL \cdot min^{-1} \cdot kg^{-1}$)	Peak Power (Watts)	S_aO_2max (%)
AC	3.89	57.2	381	92.4
AS	4.72	64.3	500	93.0
BG	4.14	53.2	389	95.5
CA	5.15	66.7	450	90.0
CJ	4.25	69.7	410	91.5
DL	4.68	49.5	418	95.0
FH	4.38	64.1	415	91.3
FM	4.34	55.9	404	93.8
JG	4.82	51.3	445	90.4
JV	5.23	66.6	500	91.7
KR	4.44	50.3	430	93.2
MF-W	4.81	66.2	475	89.1
MF-J	4.60	67.6	475	90.3
MS	4.55	56.2	435	90.3
MT	4.68	66.6	475	92.3
MW	3.83	58.2	396	94.9
NG	4.67	60.2	412	91.1
PK	4.58	54.2	450	93.2
RH	4.86	60.2	445	92.8
RM	4.89	62.0	450	91.5
TC	5.01	58.7	465	91.8
TG	4.80	59.1	445	91.9

TR	5.59	60.8	488	91.9
TS	4.86	74.9	410	94.4
mean ± SD	4.66 ± 0.40	60.6 ± 6.5	440 ± 34	92.2 ± 1.7

Values are means ± SD.

Table 34 $\dot{V}_{O_2max}$, peak power output, and lowest arterial hemoglobin saturation during maximal cycle ergometer test, group data.

GROUP	$\dot{V}_{O_2max}$ ($L \cdot min^{-1}$)	$\dot{V}_{O_2max}$ ($mL \cdot min^{-1} \cdot kg^{-1}$)	Peak Power (Watts)	S_aO_{2max} (%)
UNFIT, NORMAL (n = 8)	4.34 ± 0.34	54.7 ± 3.6	414 ± 26	93.7 ± 1.3
UNFIT, EIH (n = 2)	4.69 ± 0.19	53.8 ± 3.5	440 ± 7	90.4 ± 0.1
FIT, NORMAL (n = 11)	4.83 ± 0.37	64.4 ± 4.8	452 ± 36	92.1 ± 1.0
FIT, EIH (n = 3)	4.85 ± 0.28	66.8 ± 0.7	467 ± 14	89.8 ± 0.6

Values are means ± SD. Groups are UNFIT, ($\dot{V}_{O_2max} < 5.00$ $L \cdot min^{-1}$ or 60.0 $mL \cdot min^{-1} \cdot kg^{-1}$); FIT, ($\dot{V}_{O_2max} \geq 5.00$ $L \cdot min^{-1}$ or 60.0 $mL \cdot min^{-1} \cdot kg^{-1}$); NORMAL, ($S_aO_{2max} >$ 91.0 %); EIH, ($S_aO_{2max} \leq 91.0$ %).

Table 35 $\dot{V}_{O_2TH}$, and power output at $\dot{V}_{O_2TH}$, individual subject data.

Subject	$\dot{V}_{O_2TH}$ ($L \cdot min^{-1}$)	$\dot{V}_{O_2TH}$ ($mL \cdot min^{-1} \cdot kg^{-1}$)	Power at $\dot{V}_{O_2TH}$ (Watts)
AC	2.98	43.8	260
AS	3.20	43.6	310
BG	2.26	29.0	200
CA	3.50	45.3	280
CJ	2.73	44.8	250
DL	3.23	34.1	250
FH	2.74	40.1	238
FM	3.03	39.0	275
JG	2.98	31.7	255
JV	3.50	44.5	325
KR	3.10	35.2	270
MF-W	2.60	40.0	270
MF-J	2.93	43.1	280
MS	3.08	38.0	275
MT	2.84	34.7	280
MW	2.81	42.7	280
NG	3.00	39.3	234
PK	2.96	35.0	265
RH	3.35	41.4	280
RM	2.90	36.8	245
TC	3.30	38.7	290
TG	3.12	38.4	275
TR	3.84	41.8	310

TS	3.20	49.3	275
mean ± SD	3.05 ± 0.33	39.6 ± 4.8	270 ± 27

Values are means ± SD.

Table 36 $\dot{V}O_2TH$, and power output at $\dot{V}O_2TH$, group data.

GROUP	$\dot{V}_{O_2TH}$ ($L \cdot min^{-1}$)	$\dot{V}_{O_2TH}$ ($mL \cdot min^{-1} \cdot kg^{-1}$)	Power at $\dot{V}_{O_2TH}$ (Watts)
UNFIT, NORMAL (n = 8)	2.94 ± 0.30	37.2 ± 4.8	259 ± 26
UNFIT, EIH (n = 2)	3.03 ± 0.07	34.9 ± 4.5	265 ± 14
FIT, NORMAL (n = 11)	3.15 ± 0.15	41.4 ± 4.1	276 ± 31
FIT, EIH (n = 3)	3.01 ± 0.46	42.8 ± 2.7	277 ± 6

Values are means ± SD. Groups are UNFIT, ($\dot{V}_{O_2max} < 5.00$ $L \cdot min^{-1}$ or 60.0 $mL \cdot min^{-1} \cdot kg^{-1}$); FIT, ($\dot{V}_{O_2max} \geq 5.00$ $L \cdot min^{-1}$ or 60.0 $mL \cdot min^{-1} \cdot kg^{-1}$); NORMAL, ($S_aO_{2max} >$ 91.0 %); EIH, ($S_aO_{2max} \leq 91.0$ %).