Pulmonary Edema and the Development of Exercise-Induced Hypoxemia In Highly Trained Endurance Athletes

by

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ABSTRACT:

Twelve healthy male endurance trained athletes (mean age=24.8 $\pm$ 3.3 yrs, ht.=181.4 $\pm$ 4.8 cm., wt.=75.3 $\pm$ 6.7 kg., VO_2max=67.9 $\pm$ 5.6 ml/kg/min) served as subjects in an experiment to examine the effects of changing plasma volume on the relationship between pulmonary diffusion capacity (DLCO) and arterial blood oxygen saturation (%SaO_2) following intense exercise. Subjects were divided into two groups based on the minimum %SaO_2 recorded (HP47201A ear oximeter) during a VO_2max test; Non-desaturaters (ND=4) %SaO_2>91.0 and Desaturaters (D=8) %SaO_2<91.0. Each subject performed two, 5 minute bouts of exercise on separate days (Mijnhardt electrically-braked cycle ergometer) at a floating workload (mean=370 $\pm$ 30 W) assigned to maintain a VO_2 equal to 90% of the subjects previously determined VO_2max. The two trials (PLACEBO and LASIX) were assigned in random, double blind manner. In each of the trials the percent change in plasma volume (%dPV) was measured using hematocrit and hemoglobin values from 3cc blood samples taken immediately prior to each DLCO test. The DLCO (single-breath carbon monoxide method) was measured at three points during each trial; immediately prior to ingestion of the capsule, three hours later (one half hour prior to exercise) and one hour after completion of the exercise bout. The %SaO_2 was monitored throughout the exercise period. In the PLACEBO trial both groups showed no significant changes in either %dPV or bodyweight. There was also no significant change in Pre-Pill to Pre-Exercise DLCO but a significant decrease ($p<.05$) in DLCO after exercise did occur for both groups. The ND had a decrease of 7.34% (41.75 $\pm$ 5.43 to 38.69 $\pm$ 4.87) while the D had a 6.49% decrease in DLCO (40.13 $\pm$ 5.36 to 37.52 $\pm$ 4.29). There was no significant difference in the degree or pattern of change in DLCO following an exercise bout of this nature. The

$\%SaO_2$ showed a significant 6.54% decrease during intense exercise ($p<.001$). The ND had a 4.67% decrease in $\%SaO_2$ (97.9 ± 0.24 to 93.3 ± 1.26) while the D had a significantly greater decrease of 7.47% (97.5 ± 0.91 to 90.2 ± 1.01) ($p<.05$).

In the LASIX trial (40 mg furosemide) there was a significant 6.26% decrease in %dPV ($p<.001$) and a 1.7 ± 0.44 kg ($p<.05$) in bodyweight with no differences between ND and D. There was an overall significant decrease in DLCO values for D of 10.87% (40.84 ± 4.27 to 36.40 ± 4.82, $p<.001$) and 8.04% for the ND (40.16 ± 2.52 to 36.93 ± 3.74, $p<.01$). Both the ND and D experienced significant and similar Pre-Pill to Pre-Exercise decreases in DLCO (ND=6.27%; D=4.67%, $p<.01$). The Pre-Exercise to Post-Exercise decrease in DLCO was significant for D (6.43%, $p<.01$) but not for ND (1.88%). During 5 minutes of intense cycling after ingestion of LASIX the D experienced a significant 7.76% decrease in $\%SaO_2$ (96.9 ± 0.85 to 89.4 ± 1.19, $p<.001$) but the 3.03% change in $\%SaO_2$ for the ND was not significant.

The correlations between percent decrease in $\%SaO_2$ and percent decrease in DLCO for ND and D in both trials were non-significant. As well, there was no significant difference between the magnitude of decrease in DLCO in the PLACEBO or LASIX conditions for both groups. Intense exercise results in a decrease in Post-Exercise DLCO which may indicate the formation of subclinical pulmonary edema. The reduction in plasma volume of the magnitude observed in this study after ingestion of 40mg of LASIX did not attenuate the significant decrease in Post-Exercise DLCO or the decrease in $\%SaO_2$ experienced by the D during intense exercise. Based on the comparison of values of $\%SaO_2$ and DLCO in both ND and D, it appears that the contribution of the changes in DLCO to the drop in $\%SaO_2$ during exercise is low.

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LIST OF SYMBOLS:

a	arterial
A	alveolar
A-a	alveolar-arterial gradient
D	desaturaters
DLCO	pulmonary diffusion capacity for carbon monoxide
Dm	membrane diffusion capacity
EIH	exercise-induced hypoxemia
EIPH	exercise-induced pulmonary hemorrhaging
$FEV_{1.0}$	forced expiratory volume in the first second of expiration
FVC	forced vital capacity
Hb	hemoglobin
Hct	hematocrit
HR	heart rate
MVV	maximal voluntary ventilation
ND	non-desaturaters
PAP	pulmonary arterial pressure
PE	pulmonary edema
PO_2	partial pressure of oxygen
PV	plasma volume
Q	cardiac output
$\%SaO_2$	percent saturation of arterial blood with oxygen
V_A/Q	ventilation-perfusion ratio
Vc	pulmonary capillary volume
Ve	ventilation during exercise
VO_2max	maximal oxygen consumption

1.0 INTRODUCTION:

There is increasing evidence that a limitation to maximal aerobic exercise may arise within the lung (Dempsey, et al., 1984; Wagner et al., 1989). Reduced arterial oxygen content (CaO_2) has a direct effect on maximal oxygen consumption (VO_2max) and thus reduces endurance performance (Ekblom, 1986; Welch, 1987). Studies that have compared trained and untrained individuals demonstrate that only the highly trained (HT) endurance athletes develop a significantly reduced arterial blood oxygen saturation ($\%SaO_2$), (Rowell et al., 1964). During intense exercise over 50% of HT athletes have been observed to develop exercise induced hypoxemia (EIH) or a $\%SaO_2$ of less than 91% (Powers et al., 1988).

A widely held hypothesis is that exercise-induced hypoxemia (EIH) in highly trained athletes is primarily the result of a non-compensatory hypoventilation (Dempsey et al., 1984; Dempsey, 1986; Perrault et al., 1991). Hypoventilation indicates a reduced drive to breath and not a true mechanical limitation to increased ventilation (Dempsey, 1986). Interestingly, EIH has also been shown to occur in highly trained endurance athletes that ventilate at very high levels during maximal exercise (Hopkins and McKenzie, 1989). This raises the question of whether there is efficient exchange of oxygen across the alveolar-capillary membrane in all athletes during maximal exercise conditions.

A widening alveolar-arterial oxygen difference $(A\text{-}a)DO_2$ is an indicator of less efficient pulmonary O_2 exchange (Powers et al., 1991). The changes in $(A\text{-}a)DO_2$ that are observed during moderate exercise at sea level can be accounted for primarily by a concommitant increase in the ventilation-perfusion ratio (V_A/Q), (Gale et al., 1985; Torre-Bueno et al., 1985). Beyond a VO_2 of 3.5 l/min. though, the widening $(A\text{-}a)DO_2$ could only be accounted for by a diffusion

limitation to oxygen exchange across the alveolar-capillary membrane (Hammond et al., 1986). Two possible factors have been considered. A number of investigators have speculated that faster erythrocyte pulmonary capillary transit times (t_C) may provide an explanation for a diffusion limitation to pulmonary oxygen exchange (West et al., 1961; Dempsey, 1986; Persson et al., 1987; Capen et al., 1990). Another possibility may be that the accumulation of interstitial fluid after intense exercise may disrupt efficient pulmonary diffusion capabilities. A lingering, increased post-exercise V_A/Q ratio may reflect the accumulation of interstitial fluid in the lung (Schaffartzik et al., 1992).

In human athletes, after long endurance events (180 min.) and short, intense exercise bouts (<10 min.) a decreased lung diffusion capacity (DLCO), (Miles et al., 1983) and a correspondingly reduced $\%SaO_2$ (Hanel et al., 1991) can develop. The reduced DLCO may persist up to 48 hours post-exercise which may reflect the occurence of a transient interstitial pulmonary edema (PE) (Rasmussen et al., 1988). More specific investigation of membrane diffusion capacity (Dm) demonstrates a reduced Dm after exercise (Miles et al., 1983; Clifford et al., 1991; Manier et al., 1991) supporting the argument that pulmonary edema (PE) can develop during or post-exercise and play a contributing role in the development of EIH.

Both HT endurance athletes and thoroughbred race horses develop high pulmonary arterial pressures (PAP) during intense exercise (Reeves et al., 1988; Erickson et al., 1990). Under conditions of high PAP, disruption of the alveolar-capillary membrane can occur leading to plasma fluid and in some cases erythrocytes moving into the alveolar spaces (West et al., 1991; Tsukimoto et al., 1991). Although it has not been documented in humans, thoroughbreds often develop pulmonary hemorrhaging after intense bursts of exercise (Raphel and Soma, 1982). A common practice that has developed within horse racing circles

is to diurese these athletes with furosemide prior to competition. Although the physiological effects of furosemide are not fully understood, this controversial practice has proven effective in improving $\%SaO_2$ and reducing both the severity and incidence of exercise-induced pulmonary hemorrhaging (EIPH) without adversely effecting performance (Manohar, 1987). Reducing plasma volume via diuresis prior to maximal exercise may improve alveolar-capillary diffusion capacity and $\%SaO_2$ by attenuating the formation of extravascular fluid in the alveolar spaces.

No study to date has examined the effects of using a diuretic prior to exercise on highly trained endurance athletes who develop exercise-induced hypoxemia. It is hypothesized that the administration of the diuretic, furosemide to HT endurance athletes prior to maximal exercise may attenuate both the development of PE and the decrease in DLCO and $\%SaO_2$ after intense exercise.

2.0 METHODS:

This study examined pulmonary diffusion capacity and arterial blood oxygen saturation before and after two maximal cycle ergometer rides. One trial was performed after ingestion of 40 mg of Lasix (furosemide) and one performed after ingestion of a Placebo (n-galactose).

Twelve male, highly trained endurance athletes served as subjects for both exercise conditions. All subjects received a written and verbal description of the experiment and provided informed consent prior to their participation in this study. The experiment received approval from the University of British Columbia, Clinical Screening Committee for Research and Other Studies Involving Human Subjects. Baseline and experimental data were collected between December 1, 1991 and April 27, 1992.

2.1 Baseline Study:

After giving informed consent, all subjects underwent two preliminary inclusion tests; a pulmonary function test (PFT) and a maximal oxygen uptake test (VO_2max). Both of these tests were performed in the laboratory on the same day. Descriptive physical characteristics included age, height and weight. The pulmonary function tests involved measurement of forced vital capacity (FVC), forced expiratory volume in the first second of expiration ($FEV_{1.0}$), $FEV_{1.0}$/FVC ratio and maximal voluntary ventilation (MVV) over 12 seconds (Medical Graphics Corporation (MGC) 2001 - Pulmonary Function Software, Minneapolis).

All exercise throughout the data collection period was performed on an electrically-braked cycle ergometer (Mijnhardt KEM-3 model, Holland).

Immediately after the PFT, a 5 minute warmup was performed at less than 100 Watts resistance prior to commencing the VO_2max test. The VO_2max test was used to determine maximal oxygen uptake by continuous sampling and analysis of expired gases (MGC-2001). Subjects inspired room air and expired into a mouthpiece through a low resistance, non-rebreathing Hans Rudolph valve. Heart rates were recorded every 15 seconds during exercise via a portable heart rate monitor (Polar Vantage XL, Finland). Throughout the exercise period arterial blood oxygen saturation was recorded using an ear oximeter (Hewlett Packard 47201A) held in place by a head band. Prior application of a vasodilator cream (Finalgon Cream, Boehringer Ingelheim) to the ear pinna increased blood flow to this region. The ear oximeter was integrated with an IBM-PS/2 utilizing a data collection software package (LABTECH Notebook; Laboratory Technologies Corporation, Maryland) for $\%SaO_2$ data acquisition every second during exercise. Five second averages of $\%SaO_2$ during the exercise period were then calculated and graphed to determine the minimum level of $\%SaO_2$ during exericse. The HP 47201A ear oximeter provides a very accurate, non-invasive determination of $\%SaO_2$ relative to direct arterial measurement (r=0.90), (Smyth et al., 1986).

The cycle ergometer was integrated with the MGC-2001 which automatically controlled the workload during the exercise period. The protocol for the initial VO_2max determination was a 30 W per minute ramp to volitional exhaustion. Other criteria used to indicate that VO_2max had been attained were; identification of a plateau in VO_2 with increasing work rate; a respiratory exchange ratio (RER) of 1.15 or greater; a plateau in heart rate. Only those subjects that achieved a VO_2max of 60 ml/kg/min or 5.0 l/min were included in the study.

2.2 Experimental Data Protocol:

Subjects that qualified for this study returned to the laboratory for the experimental trials on two subsequent weeks. Each of the trials, PLACEBO and LASIX were assigned in a randomized, double-blind manner. Subjects were instructed to eat at least 1 hour prior to the first diffusion capacity test (DLCO) test because of the prolonged period during each trial that they would need to avoid eating and drinking. Trials for each subject were performed at similar times in the day.

Each trial involved a number of steps which were clearly explained to all subjects. On each trial day each subject performed a preliminary DLCO ("Pre-Pill") at the University Hospital-UBC Site 3 hours prior to the scheduled exercise time. Following this test the first of a series of three, 3 cc blood samples was taken from the cubital vein. Subjects were then handed a pre-assigned gel tablet of either Placebo (n-galactose) or 40 mg of furosemide (LASIX) which was ingested with water. Both tablets were identical in appearance. After ingestion of the tablet subjects were asked not to drink, eat or exercise prior to their exercise trial.

One hour prior to exercise all subjects performed another DLCO test ("Pre-Exercise"). Immediately prior to exercise, blood sample #2 was taken. The subject was then permitted to commence a 10 minute warmup period on the cycle ergometer at which point they were informed what the assigned starting workload would be. The starting workload (Watts) for both experimental trials was based on the peak workload attained during the initial VO_2max test. The workload was adjusted to attain and maintain 90% of their VO_2max during each 5 minute ride. Expired gas analysis, $\%SaO_2$ and HR were monitored throughout the 5 minutes of exercise using the same methods as described for the VO_2max

test. After a 5 minute cool down period on the cycle ergometer subjects remained inactive for 15 minutes after which blood sample #3 was drawn. The final DLCO ("Post-Exercise") was performed approximately 60 minutes after the completion of exercise.

Each blood sample was drawn into a heparinized test tube and delivered to University Hospital-UBC Site within one hour for analysis of hemoglobin (Hb) and hematocrit (Hct) levels. All blood samples were analyzed using an S-Plus STKR blood analyzer for in vitro blood diagnostics (Coulter, Miami USA). Calculations of pre-exercise and pre to post exercise plasma volume changes were made using the series of three values for Hb and Hct in the following formula;

$$\%d\ PV = 100 * [Hb_B/Hb_A * (1-Hct_A*.01)/(1-Hct_B*.01)] - 100$$

Note: A=before sample, B=after sample

Inclusion of Hb ratio in a reciprocal relationship with the Hct ratio corrects for any change in red cell volume (Greenleaf et al., 1979).

All single-breath carbon monoxide diffusion capacity tests (DLCO) were performed in the Pulmonary Function Laboratory, University Hospital-UBC Site utilizing a Spinnaker-Pulmonary Function Unit (Cybermedics, Colorado USA). All DLCO's were corrected for Hb as outlined by the Cotes modification for males of the Roughton and Forster relationship (Cotes et al., 1972) :

$$DL_{corrected} = DL_{measured} * [(Hb+10.22)/(1.7*Hb)]$$

Statistical analysis of the data was performed using a repeated measures ANOVA. When an overall significant F value was achieved t-test was used to distinguish significance at particular data points.

3.0 RESULTS:

3.1 Physiological Data:

Mean values for the measured physiolgical characteristics are shown in Table 1. Ages of subjects ranged from 21 to 31 years. Pulmonary function results were normal or above normal for all subjects. Maximum oxygen consumption (VO_2max) ranged from 59.6 to 79.9 ml/kg/min (4.3 - 6.2 l/min). The high average VO_2max of this group (mean VO_2max=67.9 $\pm$ 5.4 ml/kg/min) reflects a highly aerobic subject population. Each individual was an active competitive cyclist or triathlete.

TABLE 1: DESCRIPTIVE PHYSIOLOGICAL DATA (N=12)

	MEAN + STD
AGE (years)	24.8 ± 3.2
Height (cm)	181.1 ± 4.6
Weight (kg)	75.3 ± 6.3
VO2 max (l/min)	5.1 ± 0.5
VO2max (ml/kg/min)	67.9 ± 5.4
MAX WORK (Watts)	449.6 ± 30.8
MAX HEART RATE (b/min)	190.1 ± 7.1
FVC(l)	6.4 ± 0.8
FEV1.0(l)	5.1 ± 0.6
FEV1.0/FVC	0.8 ± 0.09
MVV (l/min)	207 ± 23.9

Arterial blood oxygen saturation levels (%SaO_2) were monitored during the initial VO_2max determination. Based on the minimum recorded %SaO_2 value (5 second average), two sub-groups were identified: Non-desaturaters (ND, n=4) %SaO_2 > 91%, Desaturaters (D, n=8) %SaO_2 < 91%.

During the PLACEBO and LASIX trials there was no difference in mean Work Output performed (P; 369 $\pm$ 28 Watts, L; 370 $\pm$ 30 Watts) or the mean VO_2 maintained (P; 62.5 $\pm$ 4.2 ml/kg/min, L; 63.3 $\pm$ 4.7 ml/kg/min) for each of the 5 minute exercise bouts.

3.2 The Effect of Exercise On Pulmonary Diffusion Capacity:

The mean change in DLCO, Post-exercise is summarized in Table 2. Pulmonary diffusion capacity (DLCO) was measured using the single breath carbon monoxide method. All raw DLCO values were corrected for hematocrit and hemoglobin concentration. In each testing session the average of two DLCO trials was obtained. The Pre-Exercise DLCO was taken 60 minutes prior to the exercise bout.

TABLE 2: ARTERIAL BLOOD OXYGEN SATURATION AND DIFFUSION CAPACITY.
TRIAL: PLACEBO

SUBJECT	PRE %SaO2	MIN %SaO2	%d SaO2	PRE-EXERCISE DLCO	POST-EXERCISE DLCO	%d DLCO
N=12						
MEAN	97.6	91.2	-6.54%	40.67	37.91	-6.79%
STD	0.78	1.85		5.44	4.53	

Pre %SaO2 = Pre-exercise %SaO2.
Min %SaO2 = Minimum value of %SaO2 measured during exercise.
%d SaO2 = Percent difference in %SaO2 from Pre-exercise to minimum value.
Pre-Ex DLCO = DLCO measured 1 hour prior to beginning exercise.
Post-Ex DLCO = DLCO measured 1 hour after completion of exercise.
%d DLCO = Percent difference in DLCO from pre to post exercise.

The second DLCO (Post-Exercise DLCO) was measured 60 minutes post exercise. Nine of the twelve subjects had Pre-Exercise DLCO's that were above predicted values. The other three subjects had DLCO's that were greater than 90% of their predicted values (Appendix B:Table A2).

Figure 1 displays the change in DLCO following an intense exercise bout (>90% VO_2max) on the cycle ergometer. The mean DLCO (n=12) is reduced, post-exercise (40.67 $\pm$ 5.44 to 37.91 $\pm$ 4.53). An overall 6.79% reduction in DLCO after exercise was statistically signifcant ($p<.05$).

Table 3 summarizes the comparison of mean DLCO'S between ND (n=4) and D (n=8). The ND had a mean 7.34% decrease in Post-Exercise DLCO (41.75 $\pm$ 5.43 to 38.69 $\pm$ 4.87) and the D experienced a 6.49% reduction in DLCO after exercise (40.13 $\pm$ 5.36 to 37.52 $\pm$ 4.29). There was no statistical difference in the degree or pattern of change in DLCO between the two groups following an intense exercise bout of this nature.

TABLE 3: A COMPARISON OF ARTERIAL BLOOD OXYGEN SATURATION AND DIFFUSION CAPACITY BETWEEN NON-DESATURATERS AND DESATURATERS.

TRIAL: PLACEBO

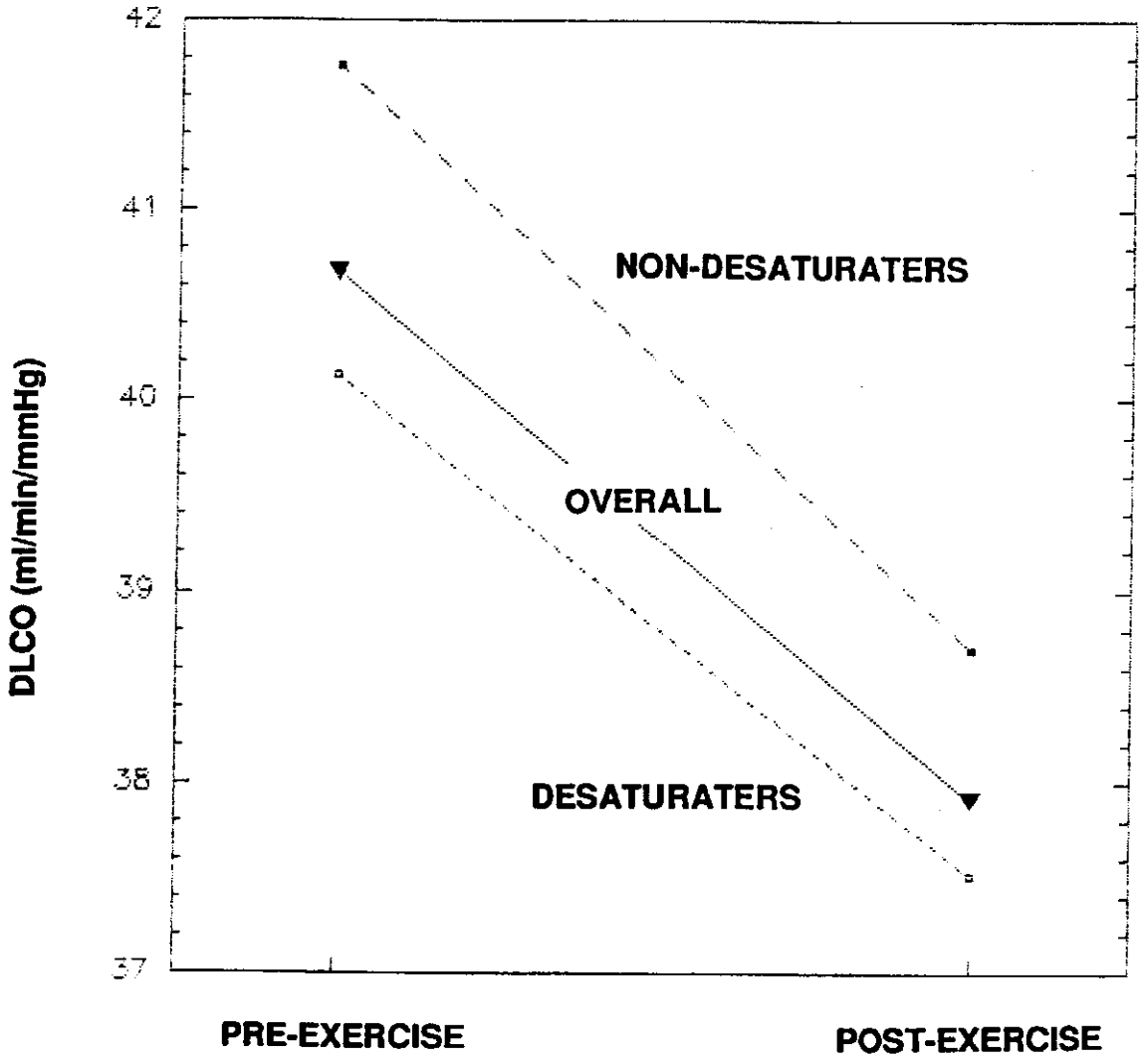
NON-DESATURATERS; n=4

SUBJECT	PRE %SaO2	MIN %SaO2	%d SaO2	PRE-EXERCISE DLCO	POST-EXERCISE DLCO	%d DLCO
MEAN	97.9	93.3	-4.67%	41.75	38.69	-7.34%
STD	0.24	1.26		5.43	4.87	

DESATURATERS; n=8

SUBJECT	PRE %SaO2	MIN %SaO2	%d SaO2	PRE-EXERCISE DLCO	POST-EXERCISE DLCO	%d DLCO
MEAN	97.5	90.2	-7.47%	40.13	37.52	-6.49%
STD	0.91	1.01		5.36	4.29	

Figure 1: PLACEBO Trial. Changes in DLCO from Pre to Post-Exercise.

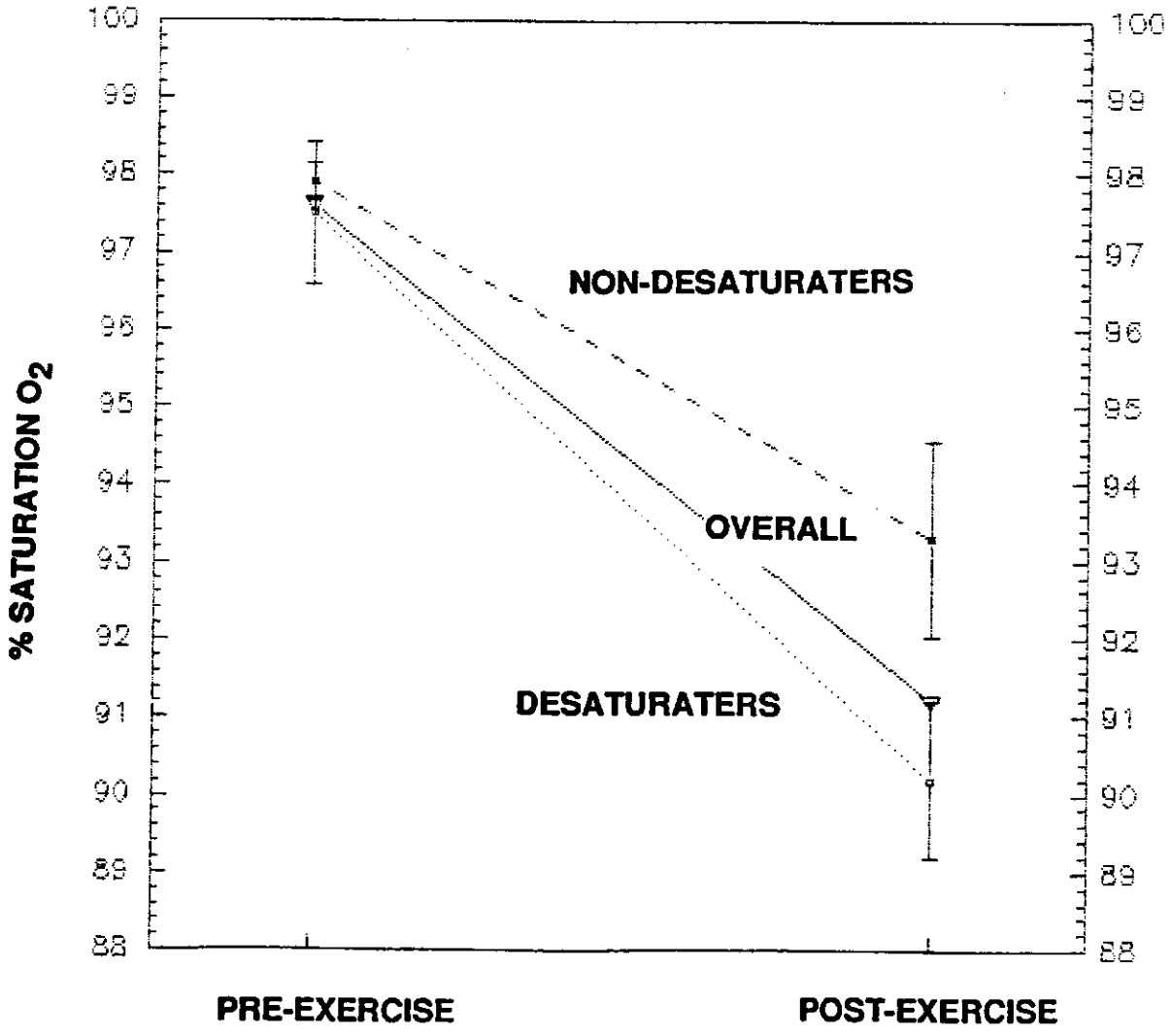


3.3 The Effect of Exercise on Arterial Blood Oxygen Saturation:

During the 5 minute exercise bout in the PLACEBO trial, changes in $\%SaO_2$ values were monitored (Table 2). The mean $\%SaO_2$ dropped from 97.6 $\pm$ 0.78 to 91.2 $\pm$ 1.85. The overall 6.54% reduction in $\%SaO_2$, seen in Figure 2, was statistically significant ($p<.001$). The Pre and minimum $\%SaO_2$ values of ND and D are also represented in Figure 2. There was no difference in mean Pre-Exercise values for $\%SaO_2$ (ND: 97.9 $\pm$ 0.24, D: 97.5 $\pm$ 0.91). The ND had a 4.67% significant decrease in $\%SaO_2$ to a mean minimum value of 93.3 $\pm$ 1.26. The 7.47%D decrease in $\%SaO_2$ (97.5 $\pm$ 0.91 to 90.2 $\pm$ 1.0) was significantly greater than in the ND ($p<.05$).

The overall trend of the relationship between percent decrease in DLCO and percent decrease in $\%SaO_2$ from pre to post-exercise was a non-significant, positive correlation ($r=.30$). In groups, ND ($n=4$) demonstrated a non-significant, negative correlation ($r=-.25$) and D ($n=8$) a non-significant, positive correlation ($r=.39$).

Figure 2: PLACEBO Trial. Changes in Arterial Blood Oxygen Saturation from Pre to Post-Exercise.



3.4 The Effect of Changing Plasma Volume and Intense Exercise on Pulmonary Diffusion Capacity and Arterial Blood Oxygen Saturation:

3.4.1. Changes In % Plasma Volume and Body Weight After Ingestion of LASIX:

Each subject ingested 40 mg of LASIX (furosemide) in gelatin capsule form 3 hours prior to exercise. The calculated mean changes in percent plasma volume (%dPV) for the PLACEBO and LASIX trials are summarized in Table 4. Included are the observed overall changes in body weight (kg) during each trial.

TABLE 4: OVERALL CHANGES IN % PLASMA VOLUME IN THE PLACEBO AND LASIX TRIALS.

	PRE-EXERCISE %d PLASMA VOLUME	POST-EXERCISE %d PLASMA VOLUME	TOTAL %d PLASMA VOLUME	WEIGHT LOSS (kg)
TRIAL: PLACEBO N=12				
MEAN	-0.35%	-1.93%	-2.28%	0.66
STD	1.69%	2.01%		0.50
TRIAL: LASIX N=12				
MEAN	-4.31%	-2.01%	-6.32%	1.67
STD	2.69%	1.60%		0.59

PRE-EXERCISE %dPV = Change in %PV from Pre-Pill to Pre-Exercise.
POST-EXERCISE %d PV = Change in %PV from Pre-Exercise to Post-Exercise.
TOTAL %d PV = Combined Pre-Exercise and Post-Exercise changes in plasma volume.

Comparing ND and D in the PLACEBO trial, neither the %dPV (-3.84 $\pm$ 0.65 vs -1.52 $\pm$ 2.07) nor the Weight Loss (0.66 $\pm$ 0.50 vs 0.76 $\pm$ 0.54) were

significant decreases (Table 5). During the PLACEBO trial %dPV ranged from 0.80 to -4.32%. Individual %dPV, calculated using Hct and Hb values, are included in Appendix B: Table A9. Subjects #4 and #5 had a slight increase in %PV based on the formula of Greenleaf et al. (1979).

TABLE 5. A COMPARISON OF CHANGES IN PLASMA VOLUME BETWEEN ND AND D IN THE PLACEBO AND L

TRIAL: PLACEBO (N=12)

SUBJECT	PRE-EXERCISE %d PLASMA VOLUME	POST-EXERCISE %d PLASMA VOLUME	TOTAL %d PLASMA VOLUME	WEIGHT LOSS (kg)
NON-DESATURATERS				
MEAN	-1.14%	-2.68%	-3.82%	0.66
STD	1.05%	1.59%		0.50
DESATURATERS				
MEAN	0.04%	-1.58%	-1.54%	0.76
STD	1.81%	2.07%		0.54

TRIAL: LASIX (N=12)

SUBJECT	PRE-EXERCISE %d PLASMA VOLUME	POST-EXERCISE %d PLASMA VOLUME	TOTAL %d PLASMA VOLUME	WEIGHT LOSS (kg)
NON-DESATURATERS				
MEAN	-3.82%	-2.55%	-6.37%	1.57
STD	3.33%	0.69%		0.83
DESATURATERS				
MEAN	-4.56%	-1.75%	-6.31%	1.71
STD	2.27%	1.83%		0.44

During the LASIX trial %dPV ranged from -0.71 to -11.56%. Both the mean %dPV (-6.32) and the Weight Loss (1.67 $\pm$ 0.59 kg) during the LASIX trial were significant reductions ($p<.05$, $p<.001$ respectively). In the LASIX trial there was no statistical difference between the %dPV of ND and D (-6.37% vs -6.31%)

or the Weight Loss (1.57 $\pm$ 0.83 vs 1.71 $\pm$ 0.44) between these two groups.

The total decrease of %PV and body weight in the LASIX trial were significantly different ($p<.05$) from those changes observed during the PLACEBO trial (Table 4). Overall, there was a significantly greater Pre-Exercise %dPV in the LASIX trial (-4.31 $\pm$ 2.69%) than in the PLACEBO trial (-0.35 $\pm$ 1.69%), ($p<.05$). The Post-Exercise %dPV were very similar between trials (P; -1.93 $\pm$ 2.01% vs L; -2.01 $\pm$ 1.60%).

3.4.2. Changes in DLCO After Ingestion of LASIX:

Overall mean changes in DLCO (n=12) during the LASIX trial are summarized in Table 6. Figure 3 graphically describes the changes in the three DLCO tests over the course of the LASIX trial.

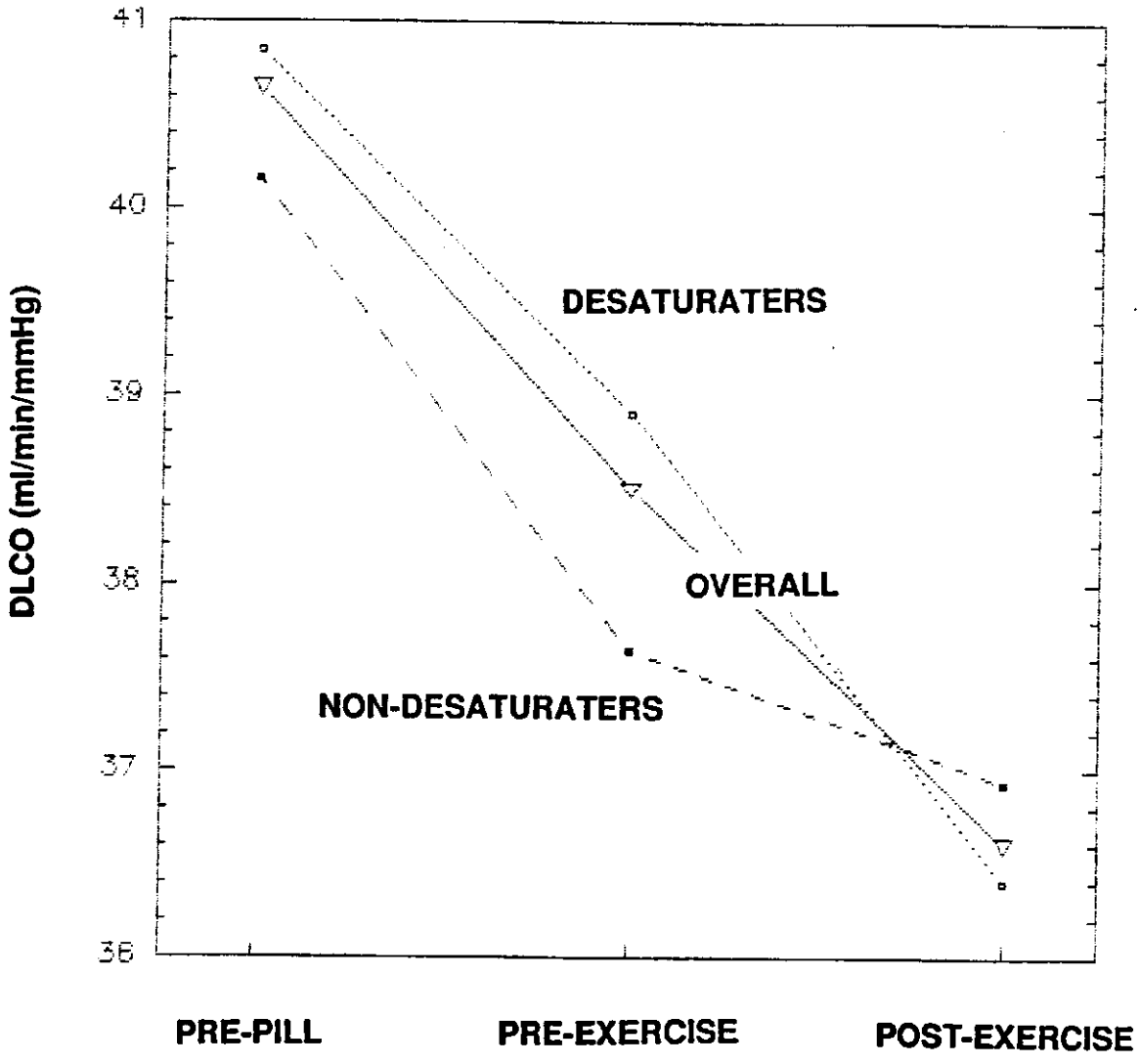
TABLE 6: ARTERIAL BLOOD OXYGEN SATURATION AND DIFFUSION CAPACITY.

TRIAL: LASIX

SUBJECT N=12	PRE %SaO2	MIN %SaO2	%d SaO2	PRE-PILL DLCO (n=7)	PRE-EXERCISE DLCO (n=12)	%d DLCO	POST-EXERCISE DLCO (n=12)	%d DLCO	TOTAL %d DLCO
MEAN	97.1	91.1	-6.18%	40.64	38.50	-5.27%	36.60	-4.95%	-9.94%
STD	0.74	2.59		6.25	6.25		4.50		

Pre %SaO2 = Pre-Exercise %SaO2.
Min %SaO2 = Minimum value of %SaO2 measured during exercise.
%d SaO2 = Percent difference in %SaO2 from Pre-Exercise to minimum value.
Pre-Pill DLCO = DLCO measured prior to ingestion of 40mg LASIX.
%d DLCO = percent difference in DLCO from Pre-Pill to Pre-Exercise.
Pre-Exercise DLCO = DLCO measured 1 hour prior to beginning exercise.
Post-Exercise DLCO = DLCO measured 1 hour after completion of exercise.
%d DLCO = Percent difference in DLCO from Pre to Post exercise.
TOTAL %d DLCO = Total percent difference in DLCO from Pre-Pill to Post-Exercise.

Figure 3: LASIX Trial. Changes in DLCO from Pre-Pill and Pre-Exercise to Post-Exercise.



In order to monitor the effects of LASIX on pulmonary diffusion capacity a Pre-Pill DLCO measure was taken and compared to a Pre-Exercise DLCO value taken 3 hours later and then a Post-Exercise DLCO one hour later. Figure 3 describes the overall (n=12) group change in DLCO as well as the changes experienced by D and ND during the LASIX trial. There was a significant overall decrease of 9.94% in DLCO during the LASIX trial for this group (n=12) from 40.64 $\pm$ 6.25 to 36.60 $\pm$ 4.50 ($p<.001$).

Table 7 shows a comparison of the changes in DLCO values for ND and D during the LASIX trial. The D experienced an overall 10.87% reduction in DLCO (40.84 $\pm$ 4.27 to 36.40 $\pm$ 4.82). The ND experienced an 8.04% reduction DLCO (40.16 $\pm$ 2.52 to 36.93 $\pm$ 3.74) during the LASIX trial.

TABLE 7: A COMPARISON OF ARTERIAL BLOOD OXYGEN SATURATION AND DIFFUSION CAPACITY BETWEEN NON-DESATURATERS AND DESATURATERS.

TRIAL: LASIX

NON-DESATURATERS

SUBJECT N=4	PRE %SaO2	MIN %SaO2	%d SaO2	PRE-PILL DLCO (n=2)	PRE-EXERCISE DLCO (n=4)	%d DLCO	POST-EXERCISE DLCO (n=4)	%d DLCO	TOTAL %d DLCO
MEAN	97.3	94.4	-3.03%	40.16	37.64	-6.27%	36.93	-1.88%	-8.04%
STD	0.34	0.94		2.52	5.67		3.74		

DESATURATERS

SUBJECT N=8	PRE %SaO2	MIN %SaO2	%d SaO2	PRE-PILL DLCO (n=5)	PRE-EXERCISE DLCO (n=8)	%d DLCO	POST-EXERCISE DLCO (n=8)	%d DLCO	TOTAL %d DLCO
MEAN	96.9	89.4	-7.76%	40.84	38.90	-4.67%	36.40	-6.43%	-10.87%
STD	0.85	1.19		4.27	6.47		4.82		

Pre %SaO2 = Pre-Exercise %SaO2.
Min %SaO2 = Minimum value of %SaO2 measured during exercise.
%d SaO2 = Percent difference in %SaO2 from Pre-Exercise to minimum value.
Pre-Pill DLCO = DLCO measured prior to ingestion of 40mg LASIX.
Pre-Exercise DLCO = DLCO measured 1 hour prior to beginning exercise.
%d DLCO = percent difference in DLCO from Pre-Pill to Pre-Exercise.
Post-Exercise DLCO = DLCO measured 1 hour after completion of exercise.
%d DLCO = Percent difference in DLCO from Pre to Post exercise.
TOTAL %d DLCO = Total percent difference in DLCO from Pre-Pill to Post-Exercise.

There was no difference in Pre-Pill DLCO values between ND and D. Both groups experienced signifcant reductions in DLCO from Pre-Pill to Pre-Exercise measurements ($p<.05$). The mean Post-Exercise DLCO for all 12 subjects was 36.6 $\pm$ 4.5. This represented a significant 4.95% decrease from Pre-Exercise values (38.50 $\pm$ 5.67; $p<.05$). The ND had a non-signifcant 1.88% decrease of DLCO from Pre to Post-Exercise (37.64 $\pm$ 5.67 to 36.93 $\pm$ 3.74). In the D, the 6.43% decrease in DLCO from Pre-Exercise to Post-Exercise (38.90 $\pm$ 6.47 to 36.40 $\pm$ 4.82) was statistically significant ($p<.01$). There was no difference in mean Post-Exercise DLCO values between ND and D groups.

3.4.3. Changes in Arterial Blood Oxygen Saturation After Ingestion of LASIX:

Table 6 shows the mean changes in $\%SaO_2$ values during the LASIX trial. The minimum $\%SaO_2$ values ranged from a low of 88.0 to 95.8%. The mean $\%SaO_2$ dropped significantly ($p<.001$) from a Pre-Exercise value of 97.1 $\pm$ 0.74% to a mean minimum value during exercise of 91.1 $\pm$ 2.59%. Comparing groups (Table 7) the ND had non-significant 3.03% decrease in $\%SaO_2$ (97.3 $\pm$ 0.34% to 94.4 $\pm$ 0.94%). The D experienced a statistically significant 7.76% reduction in $\%SaO_2$ after exercise durin the LASIX trial (96.5 $\pm$ 0.85% to 89.4 $\pm$ 1.19%, $p<.001$). This trend is visually summarized in Figure 4.

Figure 4: LASIX Trial. Changes in Arterial Blood Oxygen Saturation from Pre to Post-Exercise.

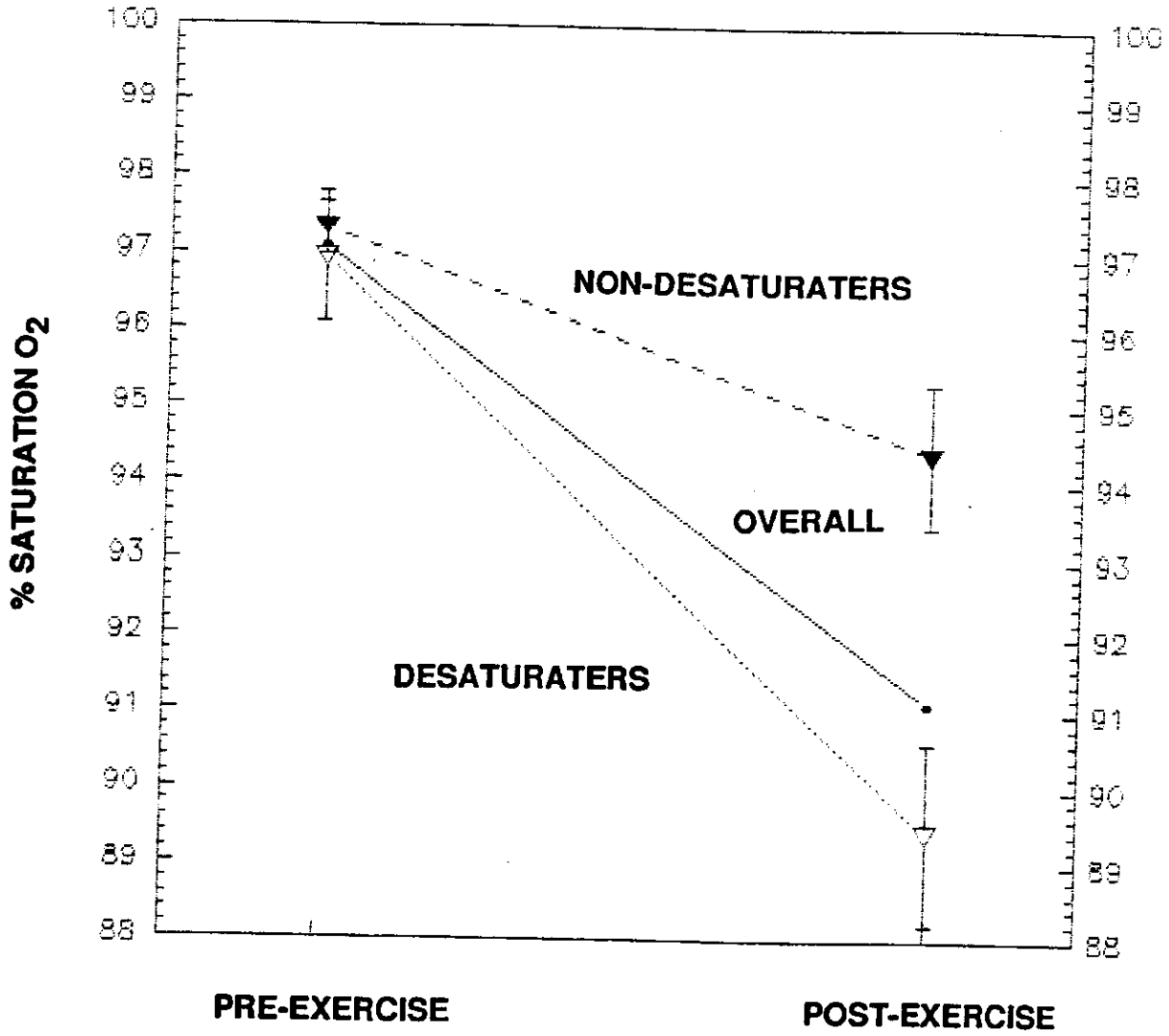


TABLE 8: SUMMARY OF CHANGES IN % PLASMA VOLUME, %SaO2 AND DLCO IN THE PLACEBO AND LASIX TRIALS.

TRIAL: PLACEBO N=12		PRE-EXERCISE (n=12)	POST-EXERCISE (n=12)	%DIFFERENCE	TOTAL %DIFFERENCE
%d PLASMA VOLUME	MEAN	-0.35%	-1.93%		-2.28%
	STD	1.69%	2.01%		
%SaO2	MEAN	97.6	91.2		-6.54%
	STD	0.75	2.19		
DLCO	MEAN	40.67	37.91		-6.79%
	STD	5.44	4.53		

TRIAL: LASIX N=12		PRE-PILL (n=7)	PRE-EXERCISE (n=12)	% DIFFERENCE	POST-EXERCISE (n=12)	% DIFFERENCE	TOTAL % DIFFERENCE
%d PLASMA VOLUME	MEAN		-4.31%		-2.01%		-6.32%
	STD		3.90%		1.60%		
%SaO2	MEAN		97.6		91.1		-6.18%
	STD		0.74		2.59		
DLCO	MEAN	40.64	38.5	-5.27%	36.6	-4.95%	-10.22%
	STD	6.25	6.25		4.5		

TABLE 9: ANOVA RESULTS - VARIABLES, GROUPS, CONDITION AND TIME.

VARIABLE	GROUP ND vs D (F,p)	CONDITION Placebo vs Lasix (F,p)	G X C (F,p)	TIME Pre vs Post (F,p)	G X T (F,p)	C X T (F,p)	G X C X T (F,p)
DLCO	0.025 (0.88)	3.22 (0.098)	0.64 (0.442)	9.98 (0.01)	0.226 (0.645)	0.83 (0.384)	0.699 (0.433)
%SaO2	106.97 (<.001)	0.39 (0.54)	2.33 (0.168)	279.3 (<.001)	29.86 (<.001)	0.765 (0.402)	1.47 (0.253)
%d Plasma Volume	1.37(.270)	9.44(<.05)	0.87(0.374)	.071(0.795)	0.182(0.678)	7.67(0.02)	0.38(0.551)
Body Weight	0.748 (0.407)	20.66 (<.001)	0.046 (0.834)				

4.0 DISCUSSION:

4.1 Changes In DLCO After Intense Exercise:

In this study significant decreases in pulmonary diffusion capacity (DLCO) and arterial blood oxygen saturation (%SaO_2) were documented in a group of twelve highly trained, male endurance athletes after intense exercise. The fitness level (VO_2max) and minimum %SaO_2 achieved by the experimental group are comparable to other studies in this area (Dempsey et al., 1984; Powers et al., 1988; Hopkins and McKenzie, 1989). These data suggest that there may be exercise situations, at sea level where oxygen transport may be limited at the lung level.

The overwhelming consensus is that the healthy lung, because of its extraordinary design, is capable of maintaining adequate oxygenation of the blood under all circumstances (Weibel, 1984). Pulmonary diffusion capacity (DLCO) has been shown to increase during exercise possibly due to an increase in pulmonary capillary blood volume (Vc) and increased membrane diffusion (Dm), (Johnson et al., 1961). In trained swimmers Magel et al. (1969) observed a linear increase in DLCO with increasing VO_2 but reported that this increase leveled off at very high work intensities. A similar pattern of increasing DLCO was also noted by Stokes et al., (1981). Increases in DLCO correlate well with increases in pulmonary arterial pressure (PAP), (Baker and Daly, 1970). Increasing PAP brings about the recruitment of pulmonary capillaries and the distension of active vessels leading to higher Vc (Vaughan et al., 1976). Trained individuals versus untrained are capable of higher maximum DLCO"s (Magel et al., 1969); the higher cardiac outputs (Q) of HT athletes leads to greater Vc.

Both the Q and Vc increase linearly with increasing exercise intensity. At

higher VO_2max (>3.5 l/min) Q continues to increase but Vc does not (Warren et al., 1991). The Q values in excess of 30 l/min achieved by somee HT athletes may overwhelm the morphological capacity of the pulmonary capillary bed. High pulmonary arterial pressures of 40 mm Hg in exercising humans (Reeves et al., 1988) and 80 mm Hg in horses (Erickson et al., 1990) have been recorded. Larger increases in V_A/Q during exercise and recovery have also been associated with individuals with higher cardiac indexes (Schaffartzik, 1992). High capillary hydrostatic pressures will increase trans-capillary fluid movement. Although interstitial fluid formation usually is managed adequately by lymph flow (Coates et al., 1984), fluid formation may exceed clearance in some extreme conditions (West 1984).

Recent research, using an animal model, looked at the effects of high pulmonary capillary on the structure of the extremely thin alveolar-capillary membrane. Pulmonary capillaries may need to endure similar wall stresses that the aorta regularly faces (West et al., 1992). Electron microscopic inspection of the tissue showed that the membrane layer increased in thickness over 100%, primarily in the interstitial region. The extremely high capillary pressures (>40 mmHg) also produced visible disruption of the endothelium of the capillary wall and epithelium of the alveolar membrane. In some instances erythrocytes were observed to be entering the alveolar spaces (Tsukimoto et al., 1991). These results provide evidence for a possible mechanism for the formation of PE during exercise.

Rasmussen et al., (1988) have observed a significant decrease in DLCO after intense exercise in HT athletes. Despite normalized Q, this decreased post-exercise DLCO persisted for up to two days. Pre and one hour post-exercise DLCO values were similar to the values measured in this study. Miles et al., (1983) proposed that a post-exercise decrease in DLCO that also persists for

several hours and days may reflect the development of a subclinical pulmonary edema. More specific measures of the membrane diffusing capacity (Dm) show a 29.3 % reduction in Dm in subjects who have completed a marathon (Manier et al., 1991).

4.2 Changes In Arterial Blood Oxygen Saturation After Intense Exercise:

Aerobic exercise performance depends on the delivery of oxygen to the muscles via the blood. A reduced level of oxygen in the blood may adversely effect performance (Ekblom, 1989); conversely, an enhanced O_2 delivery can improve VO_2max (Buick et al., 1980). The body appears to be equipped with a variety of responses to maintain O_2 delivery at near resting values (Warren et al., 1990). There may be exercise conditions where these responses may be unable to cope with the demands of exercise. One of the manifestations of the inability to cope fully with the exercise demands is a signifcant decrease in $\%SaO_2$ or exercise induced hypoxemia (EIH). EIH is currently considered to be a $\%SaO_2 <$ 91% and found to occur in approximately 50% of HT endurance athletes (Powers et al., 1989). The $\%SaO_2$in HT athletes during intense exercise is inversely related (r=-.7) to VO_2max (Williams et al., 1986). This data supports earlier findings but only in the D group (r=-.66). In the ND the $\%SaO_2$ during exercise and the VO_2max had a low but positive correlation of r=0.53. Overall, the group (n=12) had a mean $\%SaO_2$ of 91.2% at maximal exercise. Eight of the twelve subjects had minimum $\%SaO_2$ lower than 91%. The overall decrease in $\%SaO_2$ of 6.54% observed during intense exercise was significant.

The group was divided into ND (min $\%SaO_2$ > 91%; n=4) and D (min $\%SaO_2$ < 91%; n=8). Despite a signifcant difference in the minimum $\%SaO_2$ there was no difference in their mean VO_2max values or their maximal work output. Warren et al. (1991) observed that an exercise decrease in $\%SaO_2$ may be balanced by a significant hemoconcentration and ultimately, O_2 delivery to the muscles is not compromised and performance not effected by reductions in $\%SaO_2$. This group (D; n=8) developed EIH according to Powers' arbitrary figure of $\%SaO_2$ < 91%. Work along these lines, using highly trained cyclists, has demonstrated that a significant performance decrement may occur in HT endurance athletes at a $\%SaO_2$<87% (Koskolou et al., 1992).

A number of possible mechanisms have been examined to explain the apparent pulmonary O_2 diffusion limitations. During high intensity exercise some HT athletes develop EIH possibly due to a non-compensatory hypoventilation (Dempsey et al., 1984). Maximal ventilations (Vemax) recorded in this group during the 5 minute rides at 90% VO_2max ranged between 144 and 213 l/min. The Vemax did not exceed measured maximum voluntary ventilations (MVV) in these subjects. Based on this data and on the minimum end-tidal CO_2 ($PetCO_2$) values during these exercise periods it does not appear that hypoventilation, according to Dempsey's (1986) definition ($PetCO_2$ > 40 mmHg) is a factor in the development of EIH in the D group of this study.

A widening alveolar-arterial oxygen difference (A-aDO_2) is an indicator of less efficient pulmonary O_2 exchange (Powers et al., 1991). The (A-a)DO_2 can increase upto 2-3 times, in a linear manner with increasing exercise intensity (Hammond et al., 1986) leading to EIH in some HT endurance athletes (Powers et al., 1988). Anatomical shunts appear to contribute very little to the increase in (A-a)DO_2 during exercise (Hammond et al., 1986; Wagner et al., 1989). The overall V_A/Q ratio increases at least 4-5 times from rest to exercise (Dempsey

and Fregosi, 1985). During exercise at sea level, up to a VO_2 of 3.0 l/min, the widening (A-a)DO_2 could be accounted for by the increase of the V_A/Q ratio (Torre-Bueno et al., 1985). At work intensities higher than a VO_2 of 3.0 l/min the V_A/Q ratio alone could not account for the increased (A-a)DO_2 (Hammond et al., 1986). Elevated V_A/Q ratios have been observed to linger even after completion of exercise and hemodynamics have normalized. This provides further evidence of an O_2 diffusion limitation across the alveolar-capillary membrane (Schaffartzik et al., 1992).

4.3 The Relationship Between Changes in DLCO and Changes in %SaO_2:

During intense exercise both DLCO and %SaO_2 have an overall parallel decrease of similar magnitude. The low correlation between %dDLCO and %dSaO_2 (r=.30) may be explained by the high intrasubject variability in DLCO values. D has a significantly lower minimum %SaO_2 during exercise than ND despite no difference in %dDLCO between these two groups. A larger overall sample size and larger individual group sample sizes may provide greater power in discerning possible differences in the degree of change in DLCO after intense exercise. Although it is difficult to reconcile the poor relationship between %dSaO_2 and %dDLCO in the ND it is still tempting to speculate that on the basis of some of the individual data, PE contributes to EIH in some HT athletes.

Eight of the twelve HT athletes examined in this study developed EIH. Three of the eight subjects in the D group had large percent changes in DLCO (mean=-17.7%) and %SaO_2 (mean=-9.1%). The other five subjects in this group appeared to have a distinctly smaller percent change in DLCO (mean=-2.3%) and %SaO_2 (mean=-6.9%). Although these group sizes are extremely small

there is a higher correlation between %dDLCO and $\%dSaO_2$ when analyzed this way (r=.55 and r=.60, respectively). It is possible that there are differences in the morphological size of the pulmonary capillary volumes (Vc) relative to Qmax of each of these groups. Large Qmax of greater than 30 l/min achieved by some HT athletes during maximal exercise (Dempsey, 1986; Warren et al., 1991) may overwhelm the capacity of the pulmonary capillary bed and create high PAP leading to enhanced transcapillary fluid movement. Larger decreases in $\%SaO_2$ may be indicative of reduced pulmonary capillary transit times and/or reduced DLCO due the formation of PE.

4.4 Changes in % Plasma Volume, DLCO and $\%SaO_2$:

A common practice in thoroughbred horse racing is pre-race diuresis of these animals with furosemide. Pre-race diuresis attenuates the frequency and severity of exercise-induced pulmonary hemorrhaging (EIPH) without altering cardiac function or adversely affecting performance (Manohar, 1987). Although the physiological mechanism of its action is not fully understood, furosemide in ponies brings about a significant decrease in plasma volume (PV) which may attenuate the rise in systolic PAP (Goetz and Manohar, 1986). Furosemide may also improve PE clearance by increasing plasma colloid osmotic pressures and not differences in hydrostatic pressures (Wickerts et al., 1991).

During the Pre-Pill to Pre-Exercise period of approximately three hours there was a significant 5.27% decrease in DLCO with no preferential effect on D or ND. LASIX does affect DLCO made evident by the a reduced DLCO during the Pre-Pill to Pre-Exercise period. DLCO, as defined by Roughton and Forster (1957), has equal contributions from Vc and Dm. The action of LASIX has an

initial vasodilatory effect and a secondary diuretic effect (Dikshit et al., 1973; Opie, 1980). The reduction in Pre-Exercise PV possibly effected Vc. Reduced Pre-Exercise DLCO after ingestion of LASIX probably reflects a reduction in Vc.

After ingestion of furosemide and 5 minutes of intense cycling during the LASIX trial there was an additional decrease in PV of 6.30%. There was however, no improvement in the total change in DLCO after intense exercise when compared to the PLACEBO trial. In the LASIX trial the Post-Exercise decrease in DLCO was similar to the Pre-Exercise decrease.

During the 5 minutes of intense cycling there was no improvement in the overall mean minimum $\%SaO_2$ value with the ingestion of LASIX. Although PAP was not measured in this study other studies have shown that maximal PAP in humans may reach 40 mmHg (Reeves et al., 1988) which is approximately half of the PAP measured in exercising thoroughbreds (Erickson et al., 1990). The stresses on the very thin alveolar-capillary membrane in this extreme exercise situation are therefore probably much higher. Reducing PV with LASIX, in the horse has proven to be effective in attenuating the decrease in $\%SaO_2$ during maximal exercise (Manohar, 1987). Although LASIX had very little effect on mean PAP during exercise, the rise in systolic PAP was attenuated (Goetz and Manohar, 1986). The effect of LASIX therefore may have a more distinct influence on the maximal PAP that these animals experience than in humans. It is also possible that the reduction in PV's achieved in this study were not physiologically significant and therefore had little effect on attenuating maximal PAP during exercise or the possible formation of PE.

4.5 Conclusions:

The results of this study indicate that during intense exercise some HT endurance trained athletes experience a significantly reduced $\%SaO_2$. Our results concur with those of Powers et al, (1989) in that at least 50% of HT endurance athletes develop EIH. As well, HT athletes have a reduced DLCO post-exercise which may indicate the formation of subclinical pulmonary edema. After ingestion of 40mg LASIX there was a signifcant reduction in PV and in Pre-Exercise DLCO. The reduction of Pre-Exercise DLCO most likely reflects a significant decrease in Vc. The Post-Exercise decrease in $\%SaO_2$ and DLCO was similar in magnitude to that in the PLACEBO trial. In this highly trained aerobic group there was wide intrasubject variability in DLCO values. Based on this data, there does not appear to be a close relationship between the percent decrease in $\%SaO_2$ and percent decrease in DLCO. Intense exercise results in a decrease in DLCO post-exercise It appears that the contribution of the changes in DLCO to the drop in $\%SaO_2$ during exercise is low.

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APPENDIX A: Review of the Literature.

1.1 SYMMORPHOSIS:

The concept of symmorphosis developed from the work of Taylor and Weibel (1981) in which they compared the oxygen delivery and utilization systems of a variety of 'athletic' and 'non-athletic' species of mammal. The concept of symmorphosis proposes a matching of oxygen (O_2) delivery to O_2 consumption which implies that the structural design of a system should be commensurate to the functional demands of that system. If more adenosine triphosphate (ATP) is needed for muscular contractions then there is an increased number of mitochondria produced, associated with enhanced O_2 utilization (Taylor et al., 1987). If more O_2 is required by the muscle then a larger lung or enhanced diffusion capacity for oxygen (DLO_2) via conducting vessels is needed to conduct O_2 (Weibel, 1983; Karas et al., 1987). It must be noted that the capacity for gas exchange in the pulmonary system may be less 'plastic' than other elements of the O_2 delivery system such as the myocardium. Therefore, the respiratory structures that are essentially non-adaptable must be 'built' with sufficient capacity to accommodate other potential adaptations that improve an animals aerobic performance during its lifetime (Lindstedt et al., 1988). In healthy human beings it appears that the 'lung-pulmonary gas exchanger' is well designed to fully oxygenate the blood (Weibel, 1983).

2.2 THE UNTRAINED, HEALTHY HUMAN DURING MAXIMAL EXERCISE:

Exercise performance for the healthy, untrained person (UT) is primarily limited by the stroke volume (SV) of the heart and arterial oxygen content (CaO_2). It has been shown that SV increases with improved conditioning (McKardle et al., 1985) and that altering CaO_2 has a direct effect on VO_2max and thus performance (Ekblom, 1986).

The pulmonary system has the capacity to fully oxygenate blood and keeps pace with the oxygen transport system. Even at maximal exercise intensities, both the partial pressure of oxygen in the alveoli (PAO_2) and arterial blood (PaO_2) are maintained at near resting values (Rowell et al., 1964). Therefore, blood remains 95-100% saturated with oxygen even at maximal exercise intensities. There are a number of physiological mechanisms, at the pulmonary level that help to maintain consistent oxygen delivery in the healthy, UT person:

1. The mechanical response of the lung going from rest to exercise allows for a highly efficient increase in alveolar ventilation (VA) with substantial reserve available to increase in ventilation (VE) during maximal exercise. Maximum flow rates achieved during exercise tidal breathing are well within the maximum possible flow rates at rest. As well, inspiratory pleural pressures reach only 50% of the estimated capacity for pressure generation. (Johnson and Dempsey, 1992). The increased ventilation or compensatory hyperventilation is sufficient to maintain the PAO_2 greater than 110 mmHg and to remove excess carbon dioxide (CO_2). This provides a favourable O_2 gradient from the alveoli to the blood (Brooks and Fahey, 1984).

2. The diffusion capacity of the lung increases with increasing work intensity (Baker and Daly, 1970; Fisher and Cerny, 1982; Reeves, et al., 1988).

Recruitment of vessels (Capen et al., 1990) and expansion of vessels already being used in the pulmonary vascular bed (Vaughan et al., 1976) allows for a 2-3 times increase in pulmonary vascular volume (Vc), (Johnson et al., 1960; Dempsey and Fregosi, 1985).

3. At rest, transit times (t_c) for erythrocytes (RBC) passing through the pulmonary vasculature is about 0.75 seconds (Johnson et al., 1960). During exercise t_c is longer than the 0.25 seconds required for complete equilibration of O_2 across the alveolar-capillary membrane (West, 1984). Therefore, there appears to be a built in 'buffer' for RBC transit time passing through the pulmonary capillary bed.

4. The lymphatic system is effective at clearing fluid from the interstitial spaces preventing formation of extravascular fluid in the lungs secondary to increased Q and pulmonary arterial pressure (PAP) (Coates et al., 1984). Extravascular fluid in the lung may increase O_2 diffusion distances across the alveolar-capillary membrane.

5. The distribution of ventilation-perfusion ratios (V_A/Q) becomes more uniform going from rest to exercise (Bake et al., 1974). Overall V_A/Q ratio rises substantially minimizing chances of arterial hypoxemia (Johnson and Dempsey, 1992).

2.3 WELL TRAINED ATHLETES AT MAXIMAL EXERCISE:

Some HT athletes, unlike healthy UT athletes, develop a significantly reduced $\%SaO_2$ or hypoxemia at maximal exercise (Rowell et al., 1964; Dempsey et al., 1984). Despite an efficient pulmonary gas exchange system, Powers et al., (1988) have shown that exercise-induced hypoxemia (EIH), currently defined as a $\%SaO_2$ of less than 91% may occur in over 50% of HT

athletes. Williams et al. (1986) showed that PaO_2 and $\%SaO_2$ in highly trained (HT) endurance athletes during heavy exercise is inversely related to VO_2max.

2.3.1 POSSIBLE CAUSES FOR EIH:

Highly trained athletes exercising at sea level have demonstrated different ventilatory 'strategies' to achieve high VO_2max values of 4.5-5.0 l/min. (Dempsey et al, 1986). The alveolar-arterial O_2difference, (A-a)DO_2, can increase up to 2-3 times, in a linear manner, with increasing exercise intensity (Hammond et al., 1986) leading to EIH in some HT endurance athletes (Powers et al., 1988, Wagner et al., 1989). This may be explained by several apparent limitations in the pulmonary system:

1. An anatomical shunt.
2. An increase of the Ventilation:Perfusion ratio (V_A/Q).
3. Hypoventilation.
4. A diffusion limitation.

2.3.1.1. SHUNTS AND VENTILATION-PERFUSION RATIOS:

Exercise studies on thoroughbred race horses have shown that these athletes also develop a widening (A-a)DO_2 and EIH which can be attributed to a diffusion limitation with little contribution due to shunting (Wagner et al., 1989). It is now generally accepted that the overall V_A/Q ratio increases up to 4.5 times from rest to exercise (Dempsey and Fregosi, 1985; Hammond et al., 1986). Gledhill et al. (1978) found that dense gas breathing during exercise highlighted an intraregional V_A/Q inhomogeneity in the normal lung. During exercise at sea level, up to a VO_2 of 3.0 l/min., the widening (A-a)DO_2 could be accounted for by

the increased V_A/Q ratio (Torre-Bueno et al.,1985). The increased V_A/Q ratio during exercise at altitude may be due to inhomogeneous hypoxic vasoconstriction. This is supported by improved the V_A/Q ratios when breathing 100% O_2. Other factors though, are involved at sea level because no improvement of the V_A/Q ratio is observed when breathing pure O_2. Beyond a VO_2 of 3.5 l/min., the increasing (A-a)DO_2 was primarily due to a diffusion limitation (Hammond et al., 1986). Schaffartzik et al., (1992) examined the V_A/Q distribution during exercise and recovery. The group who demonstrated elevated V_A/Q during exercise also had a higher cardiac index which may lead to higher pulmonary arterial pressures (PAP). Greater V_A/Q inequality in exercise and persistence in recovery may indicate transvascular fluid movement or the formation of pulmonary edema.

2.3.1.2 HYPOVENTILATION:

At maximal exercise intensities, some athletes show a non-compensatory hypoventilation despite significant stimuli to breathe. These stimuli include increased $PaCO_2$, body temperature, blood catecholamine levels, metabolic acidosis and decreased PaO_2 (Dempsey et al., 1984). Does this imply that, for some athletes, ventilatory muscle fatigue could potentially limit maximal ventilation (Vemax) during high intensity exercise (Bye et al.,1983)? According to Dempsey (1986) the ventilatory muscles are the only truly 'essential' skeletal muscles in the body. Biochemical and histological analysis of the diaphragm indicates that the increased capillarization, number of mitochondria and the capacity to metabolize lactic acid are adaptations for highly aerobic work. Reflecting the high metabolic demand placed on the ventilatory muscles,

Manohar (1986) noted a 23 fold increase in the diaphragmatic blood flow of horses during exercise. Remarkably, the ventilatory muscle oxygen consumption ($\dot{V}O_{2resp}$) can represent about 25% of overall VO_2max translating into a $\dot{V}O_{2resp}$ of approximately 1.0 l/min. in a healthy man (Bye et al., 1983).

Can improved ventilatory muscle endurance and efficiency lead to higher maximal ventilation? Lokes et al., (1982) have shown that after running a marathon, subjects show a reduced vital capacity and/or reduced inspiratory/expiratory muscle strength. A significant glycogen depletion of diaphragm muscle may also occur after prolonged exercise in rats (Gorski et al., 1978). Specifically training the ventilatory muscles can significantly improve the endurance capacity of these muscles (Shephard, 1950; Bradley and Leith, 1978). Although the ventilatory muscles may increase their capacity for work, a number of recent studies have shown no significant improvement occurs in VO_2max or endurance performance (Fairbarn et al., 1991) Inspiratory muscle training increased mean maximal inspiratory pressure by 32% but there was no effect on other pulmonary function measures or overall VO_2max and work capacity (Hanel and Secher, 1991). This suggests that ventilatory muscle fatigue is not a limiting factor in aerobic performance at sea level.

There may be another physiological explanation for the observed non-compensatory hypoventilation. A non-compensatory hypoventilation due to a mechanical limitation may limit $V_e$max in thoroughbred race horses leading to EIH (Parks and Manohar, 1984; Art et al., 1990). Humans are oro-nasal breathers. The V_e and V_A increase in an exponential manner during exercise (McKardle and McKardle, (1989). In the horse, which is a nasal breather only, both V_e and V_A increase in a hyperbolic pattern reaching limits at higher work loads. It is believed that ventilation in horses may be limited by the obligatory entrainment of breathing pattern to stride frequency and may be due to the action

of the visceral 'piston' which is active during running (Bayly et al., 1987).

Dempsey (1986) showed that no true mechanical limitation to ventilation existed in those human athletes that demonstrated a non-compensatory hypoventilation and EIH during exercise. Breathing a less dense gas mixture of helium and oxygen ($He:O_2$), enabled these athletes to increase their $V_e$max. Augmenting Ve enabled an increase of both PAO_2 and PaO_2 and reversed the hypoxemia.

Does increasing $V_e$max improve performance? Although increasing ventilation may in turn increase the overall VO_2max of the athlete, high ventilations increase the work of breathing. The 'extra' oxygen is probably consumed by the ventilatory muscles (increased VO_{2resp}) and is not seen by the other exercising muscles. The concept of "energy stealing" (Bye et al., 1983) is supported by exercising athletes in hyperoxic conditions. Subjects that inspired hyperoxic gas mixtures demonstrate an increased PAO_2, PaO_2, CaO_2 (Ekblom, 1986) and increased VO_2max (Wilson et al., 1975; Welch, 1987) but with no increase in ventilation (Dempsey, 1986).

Dempsey's proposed model of ventilatory control provides an explanation for non-compensatory hypoventilation. Some HT athletes will, at VO_2max, attain their maximum resting voluntary flow-volume rates but, at a much lower energy expenditure. It is postulated that higher ventilations achieved by larger lung volumes would place the ventilatory muscles at a mechanically disadvantageous position leading to potential muscle fatigue. Instead, a complex network of mechanoreceptors in the ventilatory muscles, stretch receptors in the lung parenchyma and possibly flow receptors in the bronchial airways provide sensitive air flow and lung volume feedback to the brain stem during breathing. At maximal exercise intensities a lower $V_e$max is 'preferred' via this feedback despite a lower PAO_2, metabolic acidosis and a less favourable alveolar-arterial

(A-a) diffusion gradient for oxygen which can lead to hypoxemia (Dempsey, 1986). Horses, during short intense exercise will tolerate a hypercapnic state ($PaCO_2$ > 50 mmHg) and the associated metabolic acidosis for brief periods even though it is not obliged to do so by mechanical limitations on the lung or chest wall (Bayly et al., 1989). One of the possible adaptations or selective features of HT endurance athletes may be a blunted response to both hypoxia and/or hypercapnea (Saunders et al., 1976). Martin et al., (1978) though, showed there was no significant difference in exercise ventilation and chemoresponsiveness between different types of athletes. In exercising humans and horses, it is possible that the net effect of mechanical and metabolic costs to the respiratory muscles is weighed against the deleterious effects of hypoxemia on O_2 transport and acid/base imbalances in determining a ventilatory 'strategy'.

The magnitude of increased ventilation during intense exercise has been used as a major determinant of EIH (Dempsey et al., 1984). At maximal exercise, $\%SaO_2$ levels of 90% have been measured in HT endurance athletes despite substantial ventilations of over 180 l/min. (Hopkins and McKenzie, 1989). Therefore, the hypoxic ventilatory response does not necessarily provide an accurate determination of whether an athlete will develop EIH. Those athletes who develop a large $(A\text{-}a)DO_2$ and EIH, in the presence of high ventilation levels raise the question of whether efficient gas exchange occurs in the lung in all healthy humans.

2.3.1.3. DIFFUSION LIMITATIONS:

The principal of pulmonary diffusion capacity using carbon monoxide (CO) was first developed by the Kroghs in 1910. Almost 50 years later it was rediscovered by Roughton and Forster (1954) and the present day technique for

measuring pulmonary diffusion capacity was refined adding helium to the CO/air mixture (Ogilvie et al., 1957). Overall pulmonary diffusion capacity is presently described by the Roughton and Forster (1957) equation as a series of conductances of equal contribution to the overall pulmonary diffusion capacity:

$$1/DL = 1/Dm + 1/\theta Vc$$

DL represents the diffusive conductance from alveolar gas to capillary blood and has two components. The 'extra-erythrocyte' step (Dm) is the membrane diffusing capacity and involves the transfer of gas from the alveolus to the red blood cell (RBC). At the 'intra-erythrocytic' step gas enters the RBC and combines with hemoglobin (Hb) (Borland and Higenbottam, 1989). The rate of diffusion at this stage must consider both the reaction rate of the gas (O) with hemoglobin (Hb) and the pulmonary capillary blood volume (Vc). Further refinements to this equation have considered changes in Hb (Cotes et al., 1972) and COHb, PAO_2 and Hb (Frey et al., 1990). Although this equation provides the working foundation for how pulmonary diffusion capacity is monitored, disparities between physiologic and morphometric measures of lung diffusion capacity indicate that this relationship may need to be reviewed (Crapo and Crapo, 1983).

Respiratory disease states provide some understanding of the relationship between the components of the overall pulmonary diffusion capacity. Suzuki et al., (1990) examined the effect of alveolar pressure (PA) on single breath DLCO at mid-lung volumes. Patients with chronic obstructive lung disease (COPD) demonstrate reduced DLCO. They develop positive pleural pressures which constricts the pulmonary capillaries and reduces Vc with no change in Dm. Children who suffer from cystic fibrosis (CF) show no increase in DLCO whereas normals show a 27% increase going from rest to exercise. Children with CF appear to use all the available pulmonary capillary and alveolar membrane

surface area for diffusion even at rest (Zelkowitz and Giammona, 1969). Lung volume and positional changes do effect DLCO and its components. Higher pulmonary capillary blood volume (Vc) increases DLCO. Higher Vc is evident in the supine versus the sitting position and at VA greater than 60% of total lung capacity (Stam et al., 1991). According to Crystal et al., (1976) current methods of measuring DLCO though, are an insensitive diagnostic tool in interstitial lung disease demonstrated by a poor correlation between diffusion capacity and hypoxemia.

Pulmonary diffusion capacity (DL) increases linearly with increasing oxygen consumption or VO_2, reaching a plateau at higher VO_2's (Magel and Anderson,1969; Stokes et al.,1981; Perrault et al.,1991). The rapid response of DL at the onset of exercise may reflect a neural component in pulmonary vascular control during exercise (Fisher and Cerny, 1982). A less rapid rise in DL going from steady-state to higher workloads indicates that another mechanism may be involved in altering DL. Baker and Daly (1970) found a good statistical positive correlation between DL and PAP. Increasing DL during exercise is achieved by a higher membrane diffusing capacity (Dm) and pulmonary blood volume (Vc), (Johnson et al.,1960). Lung expansion during higher ventilations will recruit and expand alveoli and in turn, increase the alveolar surface area for gas exchange (Dm). Expanding pulmonary blood volume is achieved by the recruitment of vessels and the further distension of active vessels (Vaughan et al., 1976). One pulmonary adaptation to chronic hypoxia observed in Andean natives is a supra-normal DLCO. It is believed that there is an enhanced O_2 exchange interface due to a greater number of alveoli and pulmonary capillaries especially, in the bottom region of the lung (Jones et al., 1992).

At maximal exercise intensities, HT athletes are able to achieve VO_2max values of greater than 5.0 l/min. (Dempsey et al., 1984; Powers et al., 1988).

Large, HT oarsmen have achieved $V_e$max values in excess of 200 l/min. (McKenzie and Rhodes, 1981) and maximal cardiac outputs in the range of 30-35 l/min. in some HT athletes (Hopkins et al., unpubl.). At 80% of VO_2max pulmonary arterial pressures reach 38 mmHg (Reeves et al., 1988). The physical stresses placed upon this very thin (0.2u-0.4u) alveolar-capillary membrane (West, 1984) during maximal exertion situations have only recently been described (West et al., 1991; West et al., 1992).

In normoxic conditions erythrocytes require approximately 0.4 seconds in the pulmonary capillary bed for complete O_2 equilibration to occur across the alveolar-capillary membrane (West, 1984). A number of investigators propose that during maximal exercise at altitude (West et al., 1961) and at sea level (Rowell et al., 1964; Dempsey et al., 1984), t_c may be less than this critical time period necessary for complete equilibration of O_2 across the alveolar-capillary membrane. Warren et al. (1991) in their experiments demonstrated that mean red blood cell pulmonary transit time is not a primary cause of EIH in exercising humans. During exercise %SaO_2 decreased but, arterial O_2 concentration (CaO_2) was maintained at near resting values due to a significant hemoconcentration. It has been postulated that in HT athletes at high exercise intensities the maximum physiological capacity of the myocardium (Qmax) may overwhelm the morphological capacity of the pulmonary vascular bed, reduce %SaO_2 and limit VO_2max (Rasmussen et al., 1991). In an altitude acclimatization study the (A-a)DO_2 was found to have a close relationship with Q during exercise (Debout et al., 1989). After acclimatization, subjects experienced a reduced Q for any given workload. A reduction in (A-a)DO_2 and improved O_2 delivery after acclimatization may be the result of better alveolar-end capillary diffusion equilibration due to longer tc. Recent work by Hopkins et al., (unpubl.) using radio-labelled erythrocytes demonstrates that in HT endurance athletes, (A-

a)DO_2 and $\%SaO_2$ correlates more closely with t_c and Vc than with Qmax. In dogs it has been shown that Q increased 4X the resting value at maximal exercise and t_c decreased by a factor of 3X (Capen et al., 1990).

Recently, West et al., (1991) and Tsukimoto et al., (1991) presented work which shed light on the physical stresses and possible mechanisms for pulmonary diffusion impairment during intense exercise. The pulmonary vasculature of rabbits was exposed to unusually high pulmonary arterial pressures (PAP) in excess of 40 mmHg. Calculated wall stresses under these conditions demonstrated that the pulmonary capillaries must endure stresses similar to those the aorta is regularly exposed to (West and Mathieu-Costello, 1992). Electron-micrographs of the rabbit lung tissue demonstrated clearly that ultra-structural damage to the alveolar-capillary membrane had occurred consistently at these PAP's. Pulmonary capillaries bulging into alveolar spaces was observed regularly. In extreme cases, disruption of both capillary endothelial and alveolar epithelial cell layers was observed allowing erythrocytes to enter the alveolar spaces.

These findings prove interesting when considering that the PAP in thoroughbred race horses during exercise exceed 80 mmHg (Erickson et al., 1990). Marked hypertension also exists in ponies during moderate and severe exercise, and PAP increased about 250% during these conditions (Goetz and Manohar, 1986). Both hypoxemia (Bayly et al., 1987) and post-race pulmonary fluid formation and hemmorhaging (Pascoe et al., 1981; Raphel and Soma, 1982) occur frequently in thoroughbred race horses during intense exercise. Despite the high incidence, the causes of EIH and the pathophysiology of exercise-induced pulmonary hemmorhaging (EIPH) is still unclear. According to Wagner et al., (1989) most of the EIH is attributable to a diffusion limitation. EIPH may be a severe irritation of airway passages due to extreme exercise ventilations

(Raphael and Soma, 1982; O'Callaghan et al., 1987).

Is it possible that in some HT athletes that the large Qmax relative to Vc may create a situation of extreme hydrostatic pressures in the pulmonary capillaries? In humans, using an indicator dilution technique, extravascular water in the lung has been shown to increase during the early stages of exercise with no further increase later in exercise. The formation of extravascular water is thought to be a function of the redistribution of blood flow among and within the alveolar walls which increases the surface area for gas exchange and the DL of the lung (Vaughan et al., 1976). Conhaim (1989) demonstrated in dogs that alveolar flooding in hydrostatic pulmonary edema occurs across the epithelium of the alveolar ducts and respiratory bronchioles. Using a fluorescent perfusate he showed that the leak sites are large enough to be unrestrictive to plasma proteins. On the otherhand, Ehrhart and Hofman (1992) found a pressure dependent increase in lung vascular permeability to water but not to protein. During exertion at altitude the pulmonary edema observed (HAPE) is believed to be a permeability edema. This is supported by the incidence of plasma protein in fluid removed via bronchiolavage from the lung (Schoene et al., 1988). High PAP enhances the flux of fluid out of the vascular spaces. The rate of fluid formation in the interstitial spaces may exceed removal by lymph flow. Excessive buildup of fluid in the interstitial spaces may in turn force some fluid into the alveolar spaces and impair the exchange of O_2 across the alveolar-capillary membrane by increasing O_2 diffusion distances. Tsukimoto et al. (1991) noted that the thickness of the blood-gas barrier in the rabbit lung when exposed to high PAP increased almost three times. This increased thickness was primarily a result of the increased thickness of the interstitium.

Physical barriers to efficient gas exchange may arise in HT athletes during maximal exercise, creating a diffusion limitation to oxygen in the lung. After both

long endurance events (180 min.) and short, intense exercise bouts (<10 min.) subjects show decreased lung diffusion capacities for carbon monoxide (DLCO), (Miles et al., 1983) and a corresponding reduced $\%SaO_2$ (Hanel et al., 1991). The reduced DLCO can persist up to 48 hours post-exercise and may reflect the occurence of a transient interstitial pulmonary edema (Rasmussen et al., 1988).

Both Vc and Dm can be indirectly calculated using repeated measures of DLCO at different partial pressures of oxygen (PO_2), (Lewis et al.,1968). This technique is based on three assumptions: varying the alveolar PO_2 does not change the Vc or Dm; DLCO is measurable with accuracy at various PO_2's; accurate values for 0 are available. More recently developed techniques using a combination of carbon monoxide and nitric oxide (NO) allow for a more accurate determination of specific membrane diffusion capacity (Dm) (Borland and Higenbottam, 1989). A reduced Dm has been observed after exercise (Miles et al., 1983; Rasmussen et al., 1991; Clifford et al., 1991) supporting the existence of PE.

If PE arises in some HT endurance athletes and possibly impairs the transfer of O_2 across the alveolar-capillary membrane how might this effect be minimized? The formation of high altitude pulmonary edema (HAPE) is believed to be primarily a result of hypoxic pulmonary vasoconstriction. Use of nifedipine, a Ca^{2+} antagonist, decreased PAP via pulmonary vasodilation and reduced the formation of edema (Oelz et al., 1989). The diuretic acetazolamide (Az), a carbonic anhydrase inhibitor, has also shown to be effective in treatment of HAPE. Although there was no change in performance time, subjects had a significantly higher Ve and improved $\%SaO_2$ with Az administration under hypoxic conditions (Schoene et al., 1983). In the clinical setting, PE occuring in patients with cardiac failure leading to impairment of pulmonary gas exchange can be alleviated by using a powerful diuretic.

A common practice within horse racing circles is pre-competition diuresis with the diuretic, furosemide (LASIX). Although the physiological mechanisms behind its actions are not fully understood this controversial practice has proven effective in reducing both the severity and incidence of EIPH without adversely effecting performance (Manohar, 1987). Furosemide has not been shown to improve VO_2max, change heart rate (HR) nor alter the overall circulatory response to severe exercise. The exercise induced increase in blood pressure was somewhat attenutated. In a study using ponies, furosemide had very little effect on the mean PAP during exercise but attenuated the rise in systolic PAP (Goetz and Manohar, 1986). In HT endurance athletes, reducing plasma volume via diuresis prior to maximal exercise may improve alveolar-capillary diffusion capacity and $\%SaO_2$ by attenuating the formation of extravascular fluid in the alveolar spaces.

APPENDIX B: TABLE A1.

DESCRIPTIVE PHYSIOLOGICAL DATA

SUBJECT	AGE (years)	HEIGHT (cm)	WEIGHT (kg)	VO2max (l/min)	VO2 max (ml/kg/min)	MAXWORK OUTPUT (Watts)	MAXHEART RATE (b/min)	FEV1.0 (liters)	FEV1.0 (%pred)	FVC (liters)	FVC (%pred)	FEV1.0 /FVC	MVV (l/min)
1	22	182	81	5.9	72.8	470	186	5.11	111%	7.44	124%	0.69	194.0
2	24	183	74	4.9	65.8	425	194	6.24	139%	7.41	128%	0.84	224.9
3	23	178	67	5.1	75.5	410	185	5.36	124%	6.07	109%	0.88	173.2
4	26	185	77	6.2	79.9	470	191	5.51	111%	6.34	107%	0.87	238.3
5	23	178	76	4.8	63.4	450	204	5.55	126%	5.81	105%	0.95	244.2
6	21	176	66	4.3	65.9	400	198	5.05	117%	5.52	101%	0.92	185.7
7	22	184	79	5.0	63.9	430	197	5.22	113%	6.39	108%	0.82	190.5
8	23	174	66	4.5	68.3	420	198	4.43	105%	6.39	121%	0.69	212.7
9	26	177	71	4.7	65.8	460	186	3.91	92%	5.26	97%	0.74	187.0
10	31	190	85	5.1	59.6	500	189	4.28	93%	5.33	87%	0.81	179.0
11	31	185	79	5.4	68.8	470	180	5.55	127%	7.12	124%	0.78	234.8
12	26	185	83	5.4	65.5	490	182	4.61	104%	7.08	123%	0.65	219.8
MEAN	24.8	181.4	75.3	5.1	67.9	449.6	190.8	5.1	113.7%	6.3	111.2%	0.8	207.0
STD	3.2	4.6	6.3	0.5	5.4	30.9	7.1	0.6	13.6%	0.7	12.3%	0.1	23.9

APPENDIX B: TABLE A2.

TRIAL: PLACEBO

SUBJECT	PRE %SaO2	MIN %SaO2	%d SaO2	PRE-EXERCISE DLCO	POST-EXERCISE DLCO	%d DLCO
1	98.8	89.2	-9.72%	48.05 (125)	47.49 (123)	-1.17%
2	98.1	91.8	-6.42%	49.98 (133)	46.83 (123)	-6.30%
3	97.9	95.3	-2.66%	41.42 (114)	37.66 (103)	-9.08%
4	98.1	90.2	-8.05%	40.58 (108)	34.79 (93)	-14.27%
5	97.1	91.7	-5.56%	37.24 (102)	37.71 (99)	-18.17%
6	97.5	93.1	-4.51%	34.74 (95)	34.09 (92)	-1.87%
7	97.1	90.1	-7.21%	38.97 (103)	37.68 (99)	-3.31%
8	96.8	88.3	-8.78%	34.50 (95)	34.67 (96)	0.49%
9	98.8	90.1	-8.81%	32.89 (92)	31.92 (88)	-2.95%
10	96.7	91.3	-5.58%	40.10 (109)	37.37 (98)	-6.81%
11	96.3	90.5	-6.02%	48.67 (135)	38.55 (106)	-20.79%
12	98.1	93.1	-5.10%	40.86 (107)	36.17 (99)	-11.48%
MEAN	97.6	91.2	-6.54%	40.67	37.91	-6.79%
STD	0.78	1.85		5.44	4.53	

NOTE:(% of predicted values)

Pre %SaO2 = Pre-exercise %SaO2.
Min %SaO2 = Minimum value of %SaO2 measured during exercise.
%d SaO2 = Percent difference in %SaO2 from Pre-exercise to minimum value.
Pre-Ex DLCO = DLCO measured 1 hour prior to beginning exercise.
Post-Ex DLCO = DLCO measured 1 hour after completion of exercise.
%d DLCO = Percent difference in DLCO from pre to post exercise.

APPENDIX B: TABLE A3.
TRIAL: PLACEBO

NON-DESATURATERS

SUBJECT	PRE %SaO2	MIN %SaO2	%d SaO2	PRE-EXERCISE DLCO	POST-EXERCISE DLCO	%d DLCO
2	98.1	91.8	-6.42%	49.98	46.83	-6.30%
3	97.9	95.3	-2.66%	41.42	37.66	-9.08%
6	97.5	93.1	-4.51%	34.74	34.09	-1.87%
12	98.1	93.1	-5.10%	40.86	36.17	-11.48%
MEAN	97.9	93.3	-4.67%	41.75	38.69	-7.34%
STD	0.24	1.26		5.43	4.87	

DESATURATERS

SUBJECT	PRE %SaO2	MIN %SaO2	%d SaO2	PRE-EXERCISE DLCO	POST-EXERCISE DLCO	%d DLCO
1	98.8	89.2	-9.72%	48.05	47.49	-1.17%
4	98.1	90.2	-8.05%	40.58	34.79	-14.27%
5	97.1	91.7	-5.56%	37.24	37.70	1.24%
7	97.1	90.1	-7.21%	38.97	37.68	-3.31%
8	96.8	88.3	-8.78%	34.50	34.67	0.49%
9	98.8	90.1	-8.81%	32.89	31.92	-2.95%
10	96.7	91.3	-5.58%	40.10	37.37	-6.81%
11	96.3	90.5	-6.02%	48.67	38.55	-20.79%
MEAN	97.5	90.2	-7.48%	40.13	37.52	-6.49%
STD	0.91	1.01		5.36	4.29	

APPENDIX B: TABLE A4. CHANGES IN % PLASMA VOLUME.

TRIAL: PLACEBO

SUBJECT	PRE-EXERCISE %d PLASMA VOLUME	POST-EXERCISE %d PLASMA VOLUME	TOTAL %d PLASMA VOLUME	WEIGHT LOSS (kg)
1	-0.66%	-0.34%	-1.29%	
2	0.10%	-4.03%	-4.02%	
3	-2.75%	0.01%	-2.74%	
4	0.69%	0.11%	0.80%	
5	0.72%	0.01%	0.73%	0.4
6	-1.26%	-3.06%	-4.32%	0.4
7	-0.72%	-1.43%	-2.15%	0.35
8	2.88%	-3.49%	-0.61%	0.4
9	-1.84%	1.25%	-0.59%	1.8
10	-2.86%	-3.22%	-5.88%	1.15
11	2.10%	-5.29%	-3.19%	0.45
12	-0.64%	-3.65%	-4.29%	0.35
MEAN	-0.35%	-1.93%	-2.34%	0.66
STD	1.69%	2.01%		0.50

TRIAL: LASIX

SUBJECT	PRE-EXERCISE %d PLASMA VOLUME	POST-EXERCISE %d PLASMA VOLUME	TOTAL %d PLASMA VOLUME	WEIGHT LOSS (kg)
1	-6.30%	-0.64%	-6.94%	
2	-2.10%	-3.39%	-5.49%	
3	-9.55%	-2.00%	-11.56%	2.2
4	-6.31%	-2.58%	-8.46%	1.95
5	-3.30%	-5.65%	-8.98%	1.6
6	-1.26%	-3.06%	-4.32%	0.4
7	-7.72%	0.01%	-7.73%	1.7
8	-0.70%	-0.01%	-0.71%	1.1
9	-3.18%	-0.63%	-3.81%	2.1
10	-2.66%	-3.22%	-5.88%	1.15
11	-6.31%	-1.25%	-7.56%	2.4
12	-2.37%	-1.75%	-4.12%	2.1
MEAN	-4.31%	-2.01%	-6.32%	1.67
STD	2.69%	1.60%		0.59

APPENDIX B: TABLE A5.

TRIAL: PLACEBO. CHANGES IN % PLASMA VOLUME.

SUBJECT	PRE-EXERCISE %d PLASMA VOLUME	POST-EXERCISE %d PLASMA VOLUME	TOTAL %d PLASMA VOLUME	WEIGHT LOSS (kg)
NON-DESATURATERS				
2	0.10%	-4.03%	-4.02%	
3	-2.75%	0.01%	-2.74%	
6	-1.26%	-3.06%	-4.32%	0.4
12	-0.64%	-3.65%	-4.29%	0.35
MEAN	-1.14%	-2.68%	-3.84%	0.66
STD	1.05%	1.59%		0.50
DESATURATERS				
SUBJECT	PRE-EXERCISE %d PLASMA VOLUME	POST-EXERCISE %d PLASMA VOLUME	TOTAL %d PLASMA VOLUME	WEIGHT LOSS (kg)
1	-0.66%	-0.34%	-1.29%	
4	0.69%	-0.11%	0.80%	
5	0.72%	-0.01%	0.73%	0.4
7	-0.72%	-1.43%	-2.15%	0.35
8	2.88%	-3.49%	-0.61%	0.4
9	-1.84%	1.25%	-0.59%	1.8
10	-2.86%	-3.22%	-5.88%	1.15
11	2.10%	-5.29%	-3.19%	0.45
MEAN	0.04%	-1.58%	-1.54%	0.76
STD	1.81%	2.07%		0.54

APPENDIX B: TABLE A6.

TRIAL: LASIX. CHANGES IN % PLASMA VOLUME.

SUBJECT	PRE-EXERCISE %d PLASMA VOLUME	POST-EXERCISE %d PLASMA VOLUME	TOTAL %d PLASMA VOLUME	WEIGHT LOSS (kg)
NON-DESATURATERS				
2	-2.10%	-3.39%	-5.49%	
3	-9.55%	-2.00%	-11.56%	2.2
6	-1.26%	-3.06%	-4.32%	0.4
12	-2.37%	-1.75%	-4.12%	2.1
MEAN	-3.82%	-2.55%	-6.37%	1.57
STD	3.33%	0.69%		0.83
DESATURATERS				
SUBJECT	PRE-EXERCISE %d PLASMA VOLUME	POST-EXERCISE %d PLASMA VOLUME	TOTAL %d PLASMA VOLUME	WEIGHT LOSS (kg)
1	-6.30%	-0.64%	-6.94%	
4	-6.31%	-2.58%	-8.46%	1.95
5	-3.30%	-5.65%	-8.98%	1.6
7	-7.72%	0.01%	-7.73%	1.7
8	-0.70%	-0.01%	-0.71%	1.1
9	-3.18%	-0.63%	-3.81%	2.1
10	-2.66%	-3.22%	-5.88%	1.15
11	-6.31%	-1.25%	-7.56%	2.4
MEAN	-4.56%	-1.75%	-6.31%	1.71
STD	2.27%	1.83%		0.44

APPENDIX: TABLE A7.

TRIAL: LASIX

SUBJECT	PRE %SaO2	MIN %SaO2	%d SaO2	PRE-PILL DLCO	PRE-EXERCISE DLCO	%d DLCO	POST-EXERCISE DLCO	%d DLCO	TOTAL %d DLCO
1	96.2	88.4	-8.11%		50.49		46.97	-6.97%	
2	97.0	95.8	-1.24%		46.78		42.66	-8.81%	
3	97.8	94.5	-3.37%		31.68		33.04	4.29%	
4	97.5	88.0	-9.74%		30.68		32.61	6.26%	
5	98.8	88.0	-10.93%		44.37		36.31	-17.52%	
6	97.5	94.0	-3.59%	37.64	34.55	-8.21%	34.22	-0.96%	-9.09%
7	97.0	88.8	-8.45%	44.48	42.48	-4.50%	40.76	-4.05%	-8.36%
8	97.1	90.5	-6.70%	37.01	32.67	-11.73%	34.19	4.65%	-7.62%
9	96.2	90.0	-6.44%	36.02	31.78	-11.77%	31.19	-1.86%	-13.41%
10	96.1	91.3	-4.90%	39.64	39.81	0.43%	35.91	-9.82%	-9.41%
11	96.8	90.3	-6.71%	47.04	39.17	-16.73%	33.51	-14.45%	-28.76%
12	97.1	93.2	-3.92%	42.67	37.55	-12.00%	37.81	0.69%	-11.39%
MEAN	97.1	91.1	-6.18%	40.64	38.50	-5.27%	36.60	-4.95%	-9.96%
STD	0.74	2.59		3.86	6.25		4.50		

NOTE:(% of predicted values)

Pre %SaO2 = Pre-exercise %SaO2.
Min %SaO2 = Minimum value of %SaO2 measured during exercise.
%d SaO2 = Percent difference in %SaO2 from Pre-exercise to minimum value.
Pre-Ex DLCO = DLCO measured 1 hour prior to beginning exercise.
Post-Ex DLCO = DLCO measured 1 hour after completion of exercise.
%d DLCO = Percent difference in DLCO from pre to post exercise.
TOTAL %dDLCO = Total precent difference in DLCO from Pre-Pill to Post-Exercise.

APPENDIX B: TABLE A8.
TRIAL: LASIX

NON-DESATURATERS

SUBJECT	PRE %SaO2	MIN %SaO2	%d SaO2	PRE-PILL DLCO	PRE-EXERCISE DLCO	%dDLCO	POST-EXERCISE DLCO	%d DLCO	TOTAL %d DLCO
2	97.0	95.8	-1.24%		46.78		42.66	-8.81%	
3	97.8	94.5	-3.37%		31.68		33.04	4.29%	
6	97.5	94.1	-3.59%	37.64	34.55	-8.21%	34.22	-0.96%	-9.09%
12	97.1	93.2	-3.92%	42.67	37.55	-12.00%	37.81	0.69%	-11.39%
MEAN	97.3	94.4	-3.03%	40.16	37.64	-6.27%	36.93	-1.88%	-8.04%
STD	0.34	0.94		2.52	5.67		3.74		

DESATURATERS

SUBJECT	PRE %SaO2	MIN %SaO2	%d SaO2	PRE-PILL DLCO	PRE-EXERCISE DLCO	%d DLCO	POST-EXERCISE DLCO	%d DLCO	TOTAL %d DLCO
1	96.2	88.4	-8.11%		50.49		46.97	-6.97%	
4	97.5	88.0	-9.74%		30.68		32.60	6.26%	
5	98.8	88.0	-10.93%		44.37		36.31	-17.52%	
7	97.0	88.8	-8.45%	44.48	42.48	-4.50%	40.76	-4.05%	-8.36%
8	97.1	90.5	-6.70%	37.01	32.67	-11.73%	34.19	4.65%	-7.62%
9	96.2	90.0	-6.44%	36.02	31.78	-11.77%	31.19	-1.86%	-13.41%
10	96.1	91.3	-4.90%	39.64	39.81	0.43%	35.90	-9.82%	-9.43%
11	96.8	90.3	-6.71%	47.04	39.17	-16.73%	33.51	-14.45%	-28.76%
MEAN	96.9	89.4	-7.76%	40.84	38.93	-4.67%	36.43	-6.43%	-10.80%
STD	0.85	1.19		4.27	6.47		4.82		

Pre %SaO2 = Pre-exercise %SaO2.
Min %SaO2 = Minimum value of %SaO2 measured during exercise.
%d SaO2 = Percent difference in %SaO2 from Pre-exercise to minimum value.
Pre-Pill DLCO = DLCO measured prior to ingestion of 40mg LASIX.
Pre-Ex DLCO = DLCO measured 1 hour prior to beginning exercise.
%d DLCO = percent difference in DLCO from Pre-Pill to Pre-Exercise.
Post-Ex DLCO = DLCO measured 1 hour after completion of exercise.
%d DLCO = Percent difference in DLCO from pre to post exercise.
TOTAL %dDLCO = Total precent difference in DLCO from Pre-Pill to Post-Exercise.

APPENDIX B: TABLE A9. HEMOGLOBIN AND HEMATOCRIT VALUES FOR PLACEBO AND LASIX TRIALS.

		PLACEBO						LASIX					
SUBJECT		SAMPLE 1	SAMPLE 2	%dPV	SAMPLE 3	%dPV	TOTAL %dPV	SAMPLE 1	SAMPLE 2	%dPV	SAMPLE 3	%dPV	TOTAL %dPV
1	HCT	0.447	0.457	-0.66%	0.447	-0.34%	-1.29%	0.429	0.444	-6.30%	0.455	-0.64%	-6.94%
	Hb g/l	153	154		155			147	159		160		
2	HCT	0.419	0.409	0.10%	0.44	-4.03%	-4.02%	0.409	0.411	-2.10%	0.422	-3.39%	-5.49%
	Hb	144	144		150			140	143		148		
3	HCT	0.417	0.427	-2.75%	0.424	0.01%	-2.74%	0.397	0.431	-9.55%	0.434	-2.00%	-11.56%
	Hb	142	146		146			133	147		150		
4	HCT	0.436	0.427	0.69%	0.421	0.11%	0.80%	0.434	0.457	-6.31%	0.458	-2.58%	-8.46%
	Hb	148	147		147			149	159		155		
5	HCT	0.415	0.416	0.72%	0.417	0.01%	0.73%	0.432	0.451	-3.30%	0.48	-5.65%	-8.98%
	Hb	144	144		145			146	151		160		
6	HCT	0.478	0.468	-1.26%	0.463	-3.06%	-4.32%	0.464	0.462	-1.26%	0.475	-3.06%	-4.32%
	Hb	165	158		162			157	159		164		
7	HCT	0.414	0.409	-0.72%	0.409	-1.43%	-2.15%	0.428	0.458	-7.72%	0.456	0.01%	-7.73%
	Hb	137	138		140			144	156		156		
8	HCT	0.422	0.406	2.88%	0.413	-3.49%	-0.61%	0.406	0.415	-0.70%	0.42	-0.01%	-0.71%
	Hb	144	139		143			143	144		144		
9	HCT	0.468	0.464	-1.84%	0.455	1.25%	-0.59%	0.439	0.459	-3.18%	0.458	-0.63%	-3.81%
	Hb	160	163		161			153	158		159		
10	HCT	0.447	0.453	-2.86%	0.439	-3.22%	-5.88%	0.438	0.452	-2.66%	0.463	-3.22%	-5.88%
	Hb	154	151		153			147	151		156		
11	HCT	0.438	0.42	2.10%	0.449	-5.29%	-3.19%	0.442	0.467	-6.31%	0.471	-1.25%	-7.56%
	Hb	147	144		152			149	159		161		
12	HCT	0.464	0.473	-0.64%	0.487	-3.65%	-4.29%	0.488	0.489	-2.37%	0.499	-1.75%	-4.12%
	Hb	158	159		165			165	169		172		

Greenleaf et al., 1979: %dPV=100*[HbB /HbA*(1-HctA*.01)/(1-HctB*.01)]-100.
A=before sample; B=after sample.