THE EFFECT OF EXERCISE INTENSITY ON POST-EXERCISE
LUNG DIFFUSION IN HIGHLY TRAINED ATHLETES

by

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ABSTRACT

The purpose of this study was to determine the effect of exercise intensity on the post-exercise reduction of the diffusion capacity of carbon monoxide in the lung (DLco) and whether these declines were related to reductions in arterial oxyhemoglobin saturation (%SaO₂) during exercise. Ten highly trained (VO₂max = 66.8 ml·kg⁻¹·min⁻¹) males were recruited. Subjects performed a maximal cycling test to determine VO₂max and then returned on three separate occasions to perform ten minutes of submaximal cycling at 90%, 60%, and 30% of VO₂max. During each exercise session, expired gases, HR, and %SaO₂ were recorded every fifteen seconds. DLco was measured prior to exercise (baseline) and one-hour following each of the exercise sessions. DLco was partitioned into its components of diffusion capacity of the alveolar membrane (DM) and pulmonary capillary blood volume (Vc) by measuring it at two concentrations of inspired O₂. DLco significantly declined from baseline following each of the submaximal exercise sessions. The reductions following the 60% and 30% exercise sessions were similar but greater than the decline that occurred following the 90% exercise test. Reductions in post-exercise DLco were accompanied by declines in DM that reached statistical significance following the 90% and 60% tests, but not after the 30% submaximal exercise session. The decline in post-exercise Vc was also greatest following the 90% submaximal session and similar for each of the 60% and 30% tests. However, Vc reductions did not reach statistical significance following any of the exercise intensities (p=0.10). %SaO₂ during 90% submaximal exercise declined significantly greater than both the 60% and 30% exercise tests, and all were decreased below baseline. No correlation was found between the post-exercise reductions in DLco, DM, or Vc, and %SaO₂ at any of the exercise intensities. In

summary, the results suggest that measurement of post-exercise DLco at different intensities of exercise does not reflect oxygen saturation levels during each test. Furthermore, the validity of using post-exercise measurements of DLco to indirectly implicate pulmonary edema as a mechanism of EIH is questionable.

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INTRODUCTION

Traditionally, it was believed that the pulmonary system was not a limiting factor of maximal exercise at sea level and that it appeared capable of withstanding the stress of exercise (Whipp and Wasserman, 1969). However, in 1986 Dempsey hypothesized that highly-trained aerobic athletes may adapt cardiovascular capacity and skeletal muscle utilization to a point where they surpass the ability of the pulmonary system to supply adequate oxygen (O_2) to meet these demands. This has been observed to result in a reduction in PaO_2 of 21 to 35 mmHg from resting values and a reduction in the percent arterial oxyhemoglobin concentration ($\%SaO_2$) to 91.9% in highly-trained athletes exercising at maximal intensities (Dempsey et al., 1984). Since the Dempsey study, $\%SaO_2$ reductions below 91% have been found in highly-trained athletes during maximal exercise (Harms and Stager, 1995, Powers et al., 1988, Williams et al., 1986). This phenomenon is termed exercise-induced hypoxemia (EIH), and occurs in approximately 50% of highly trained athletes exercising at maximal intensities (Powers et al., 1988). EIH is of interest because the respiratory system has now been implicated in the reduced ability of some highly trained athletes to attain VO_{2max} (Powers et al., 1989) and/or maximal exercise performance (Koskolou and McKenzie, 1994).

The exact contribution of various mechanisms of EIH are unknown. Veno-arterial shunt, inadequate hyperventilation, ventilation-perfusion (V_A/Q) inequality, and diffusion limitation resulting from either decreased transit time or increased interstitial pulmonary edema have been proposed as possible contributors. However, the significance of each of these mechanisms acting alone or together is not completely understood.

The diffusion capacity of carbon monoxide in the lung (DLco) has been used as an indirect method of evaluating changes in lung diffusion (Billiet et al., 1970, Rasmussen et al., 1992). An increase in DLco has been found to occur during exercise (Billiet et al., 1970, Turcotte et al., 1997) followed by a decline post-exercise that reaches its lowest values at 6 hours followed by a gradual increase to baseline levels by 24 hours (Sheel et al., 1998). Some authors have claimed that a decline in post-exercise DLco may represent an increase in pulmonary edema that could restrict the diffusion of gases across the alveolo-capillary membrane (Caillaud et al., 1995, Miles et al., 1983, Manier et al., 1991, Rasmussen et al., 1986, 1988).

Partitioning DLco into its components of membrane diffusing capacity (DM) and pulmonary capillary blood volume (Vc) permits speculation on the mechanism of the decline in post-exercise DLco. It is believed that a post-exercise reduction in DLco accompanied by a decline in DM and not Vc is indicative of pulmonary interstitial edema which would increase the diffusion distance of alveolar gases across the alveolo-capillary membrane (Miles et al., 1983, Manier et al., 1991). One of the mechanisms believed to be responsible for pulmonary edema is membrane disruption caused by very large increases in cardiac output (Q) at high intensities of exercise. Possibly, this would stress the pulmonary capillary membrane sufficiently to cause disruptions and subsequent leakage of fluid, including plasma proteins and red blood cells (RBCs), into the alveolar spaces (Hopkins et al., 1996, West et al., 1991, 1993, Schaffartzik et al., 1993). An increase in interstitial fluid may alter blood gas homeostasis for both PaO₂ and %SaO₂. In highly-trained athletes, EIH occurs only at high intensities of exercise, and therefore, it may be expected that only these conditions could produce pulmonary edema reflected by a post-exercise reduction in DLco and DM.

If the above is true, an inverse relationship between exercise intensity and post-exercise reductions in DLco would result. As one of the mechanisms of EIH is a diffusion limitation secondary to a transient interstitial edema, a decline in post-exercise DLco only at high intensities of exercise would be caused mostly by a decline in DM. In addition, a diffusion limitation caused by pulmonary edema might also affect %SaO₂ during exercise.

Two previous studies have measured post-exercise DLco after different intensities of exercise. The first study found that DLco decreases from baseline two hours following 61% and 75% submaximal exercise (Hanel et al., 1993). Although they found no significant relationship between exercise intensity and the post-exercise decline in DLco, a trend of decreasing DLco as exercise intensity increased was noted (Hanel et al., 1993). These authors concluded that pulmonary edema was not a likely mechanism for the decline in post-exercise DLco because of the reductions found after low (61%) intensity exercise. This study did not measure %SaO₂ or partition DLco into DM or Vc.

In a second study, post-exercise DLco declined one hour after each submaximal intensity. However, the reduction following 75% of VO₂max was twice as much as the decline following 50% or 25% of VO₂max (Sharratt et al., 1996). These authors also found an inverse relationship between exercise intensity and DM, but only a main effect for time for Vc. This study did not measure %SaO₂. They concluded that the post-exercise decline in DLco appears to be related to exercise intensity with a greater influence from DM.

To date, no study has documented the relationship between post-exercise DLco and %SaO₂ at various intensities of exercise. Therefore, the purpose of this study was to determine the relationship between the reduction in %SaO₂ during exercise and the decline in post-exercise DLco, DM, and Vc, at different intensities of exercise.

Hypotheses

1. Post-exercise DLco will decrease from baseline following each exercise intensity.
2. The decline in post-exercise DLco will be inversely proportional to the intensity of exercise.
3. The decline in post-exercise DLco at each intensity will not be correlated with the lowest % arterial oxyhemoglobin desaturation (%SaO₂).
4. The post-exercise reduction in Vc will not be correlated with the lowest % arterial oxyhemoglobin value at each intensity.
5. The post-exercise decline in DM will not be correlated with the lowest % arterial oxyhemoglobin value at each intensity.
6. The decline in post-exercise Vc will be inversely proportional to the intensity of exercise and will reflect the reduction in DLco at each intensity.
7. DM will significantly decline post-exercise only after the 90% and VO₂max. exercise session. DM will not significantly decline after the 60% submaximal session or the 30% submaximal session.

METHODOLOGY

Subjects

This study was approved by the Clinical Screening Committee for Research and Other Studies Involving Human Subjects of the University of British Columbia. Ten male subjects were recruited for this study (9 cyclists and 1 triathlete). Subjects were included if they were highly trained ($\text{VO}_2\text{max} > 65 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ or $> 5.0 \text{ l}\cdot\text{min}^{-1}$), non-smokers, without any history of lung disease. For attainment of VO_2max , subjects were required to exercise to volitional fatigue and obtain 2 out of the 3 requirements as follows: an RER value > 1.10 , a plateau or decline in VO_2 as workload increased, and an achievement of 90% of age adjusted maximal heart rate. Subjects performed standard pulmonary function testing to determine resting lung volumes. For all 4 testing periods, subjects were required to abstain from exhaustive exercise for 24 prior to testing, refrain from ingestion of alcohol or caffeine for 12 hours, and food or other liquids other than water for 2 hours.

Protocol

Subjects were acquainted with the procedures and tests prior to their first testing session. Upon written consent, subjects were asked to complete 4 testing sessions. All exercise tests were performed in the exercise physiology lab at a mean temperature of 22°C (range = $19\text{-}23^\circ \text{C}$) and a barometric pressure range of 751-762 mmHg. During the first visit, subjects rested for 30 minutes in a seated position followed by measures of pulmonary lung mechanics and baseline measures of DLco. Spirometry measures were performed on a Collins PLUS DS II and included: forced vital capacity (FVC), forced expiratory volume in one

second (FEV_1), and forced expiratory flow at 25% to 75% of FVC ($FEV_{25-75\%}$). DLco was measured by a Collins Survey Tach Pulmonary Function Testing Unit (Warren E. Collins Inc., Braintree Ma.) using the equations of Roughton and Forster (1957) as modified by Ogilvie et al. (1957). The first maximal breathing test was performed using a test gas of 21% O_2 , 10% He, and 0.3% CO, in a balance of N_2 . Subjects were asked to inspire fully from residual volume, hold their breath for 10 seconds, then expire fully. During breath holding, subjects were asked to relax in order to avoid performing a Valsalva or Muller maneuver. Upon expiration, the first litre of gas was discarded and the next 750 ml was analyzed automatically by the Collins system. Subjects performed two of these tests to be sure that values were within $3 \text{ ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$, and if tests were not within this range, a third test was conducted. The reliability of this test has been shown to be high ($r = 0.96$) (Sheel et al., 1996). Subjects then breathed a 100% O_2 gas from a Douglas bag for 5 minutes through a non-rebreathing Rudolph valve (Hans Rudolph, #2700B). Following the 5 minute period of 100% O_2 breathing a second test gas containing 10% He, 0.3% CO, in a balance of O_2 , was used for a second DLco measurement in order to partition DL into DM and VC. This second test was otherwise identical to the first test. Volume calibration for both DLco and spirometry was performed prior to each test using a 3-L syringe.

Following spirometry tests and baseline DLco measures, subjects warmed-up on an electronically braked cycle ergometer (Quinton, Excalibur) for 8 minutes at a self selected power output. All 10 subjects then performed an exercise test to exhaustion using a ramp protocol beginning at 0 and increasing by $30 \text{ watts} \cdot \text{min}^{-1}$ until exhaustion. During exercise, heart rate (HR) was recorded every 15 seconds using a polar heart rate monitor (Polar Vantage XL, Finland). Expired gases were collected in a 5-L mixing chamber where gas

fractions for oxygen and carbon dioxide were sampled by an automated gas analysis system (Rayfield). The analyzers were calibrated before each test with known gases containing 10% O₂ and 5% CO₂. During exercise, subjects breathed room air through a low resistance, non-rebreathing valve (Hans Rudolph). %SaO₂ was measured and recorded by ear oximetry every 15 seconds (Ohmeda Biox 3740 pulse oximeter). To increase blood flow to the ear, the lobe was rubbed with a vasodilatory nicotine cream (Finalgon, Boehringer Ingelheim). At the conclusion of the maximal exercise session, subjects cycled for a brief time at no more than 60 watts resistance and then rested for 60 minutes in a seated position followed by post-exercise DLco measurements.

Subjects were asked to return to the laboratory once a week for 3 weeks to perform 3 randomly selected submaximal (90%, 60%, and 30% of VO₂max) exercise tests for 10 minutes. Submaximal exercise intensities were initially determined by the percentage of maximal power output accomplished during the VO₂max test. Each submaximal test was preceded by a 5 minute warm-up at less than 50% of the starting power for that particular exercise test. Subjects began the submaximal test at the specified power output which was then adjusted during the 10 minute test to ensure that the subject exercised the full 10 minutes at the specified intensity as measured by VO₂ (ml·kg⁻¹·min⁻¹). After each submaximal test, subjects rested for 60 minutes in a seated position after which a post-exercise DLco measurement was conducted using the same procedure as the baseline and post-exercise maximal test measures.

Calculation of the Diffusing Capacity of Carbon Monoxide in the Lung (DLco)

Alveolar Volume (single breath)

$$VA (sb) = \frac{He \text{ inspired}}{He \text{ expired}} \times VI \times 1.05 \times BTPS$$

where: VA = alveolar volume

VI = volume inspired

BTPS = body temperature
and pressure saturated

Diffusion of the Lung/Alveolar Volume

$$DL/VA = (60/BHT) \times (1000/PB-47) \times \ln [He \text{ expired}/CO \text{ expired}] \times (STPD/BTPS)$$

where: BHT = breath-hold time

PB = barometric pressure

STPD = standard temperature
and pressure dry

DL = diffusion capacity of the lung

Ln = natural logarithm

CO = carbon monoxide

BTPS = body temperature
and pressure saturated

Diffusion of the Lung (single breath)

$$DL (sb) = VA (sb) \times DL/VA \text{ (see above for abbreviations)}$$

Calculation of DM and Vc

By measuring DLco at two different inspired O₂ concentrations (DLco_{21% O₂} and DLco_{90% O₂}) and plotting each value of 1/DLco against each 1/θ, a linear regression line can be plotted. The slope of the line represents 1/Vc and the Y-intercept represents 1/DM.

Therefore, the resistance of DLco is represented by its reciprocal (1/DLco):

$$\frac{1}{DLco} = \frac{1}{DM} + \frac{1}{\theta \cdot Vc}$$

Theta (θ) represents hemoglobin concentration which depends on the number of red cells present upon measurement. As stated previously, 1/DLco represents the resistance of DLco.

Hence, the sum of the resistance of DLco may indicate its causative factors. Therefore, as seen above, two resistances exist: the resistance of CO to travel from the alveoli to the red

blood cell through the alveolar epithelium, basement membrane, the capillary endothelium, and plasma layer (1/DM), and the resistance of the volume of red blood cells in the pulmonary capillary bed (V_c) in conjunction with the rate of chemical reaction of CO with hemoglobin (θ). Hemoglobin was not measured in this study. The default value set for hemoglobin for each subject was 14.0 gms%, which is on the lower side for the normal male range of 13 to 17 gms%.

Alveolar Gas Equation

$$P_{AO_2} = [FIO_2 \times (PB - 47)] - P_{ACO_2} + \frac{(1 - FIO_2)}{RER}$$

where: P_{AO_2} = alveolar pressure of oxygen
 FIO_2 = fraction of inspired oxygen
 PB = barometric pressure

P_{ACO_2} = alveolar pressure of
carbon dioxide

End P_{capO_2} represents P_{AO_2} at a pressure that is 15 mmHg lower than P_{AO_2} . As determined by Forster et al. (1986), these equations use an assumed RER of 0.8 and an assumed P_{aCO_2} of 40 mmHg equal to that of estimated alveolar PCO_2 (P_{ACO_2}).

Statistical Analysis

A one (subjects) by four (time) analysis of variance with repeated measures on time was performed for each of the following variables: DLco, V_c , DM, and %SaO₂. If a significant F-ratio was observed, a Bonferroni contrast was applied post-hoc to determine the specific differences from baseline. Pearson product moment correlation coefficients were conducted to determine significant relationships between DLco, V_c , DM, and %SaO₂. The alpha level was set and adjusted for each statistical measure at a priori of $p < 0.05$.

RESULTS

General Data

The subjects in this study were of similar age ($27.5 \text{ yrs} \pm 5.3$), height ($181.2 \text{ cm} \pm 6.0$), and mass ($74.1 \text{ kg} \pm 6.0$) to previous studies that have evaluated EIH in highly trained athletes. All ten subjects completed the 4 exercise tests including the full 10 minutes of exercise at each submaximal intensity.

The actual mean values for pulmonary function tests (FVC, FEV_1 , and FEV_{25-75}) for all subjects were normal and are listed in Table 1 along with their respective predicted values. The mean observed group values for each pulmonary function test was equal to or greater than the predicted values.

Table 1. Spirometry mean predicted, mean actual, and % of predicted values.

	Mean Predicted	Mean Actual	% of predicted
FVC	5.7 (0.5)	5.7 (0.6)	100%
FEV_1	4.7 (0.4)	4.8 (0.5)	101%
$\text{FEV}_{25-75\%}$	5.0 (0.4)	5.8 (1.7)	117%

Values are means ($\pm$ Std Dev.).

Maximal Exercise

Individual values for each subject during maximal exercise are listed in Table 2. The overall decline in $\%\text{SaO}_2$ during maximal exercise was significantly decreased from baseline ($F=88.61$, $p<0.001$). Similarly, $\text{DLco}_{(21\%)}$ measured 1 hour post-exercise was significantly declined from baseline values ($F=47.60$, $p<0.001$) (Figure 1). However, the post-exercise reduction in $\text{DLco}_{(21\%)}$ was not significantly correlated with the decline in $\%\text{SaO}_2$ during

exercise ($r = 0.43$, $p=0.22$). In addition, the decline in %SaO₂ during exercise showed a moderate but non-significant correlation with VO₂max ($r= -0.56$, $p=0.09$).

Table 2. Individual and mean maximal values for heart rate (HR), minute ventilation (V_E), respiratory exchange ratio (RER), power, VO₂, and %SaO₂ for the maximal exercise session.

Subject	HR (bpm)	V _E (l·min ⁻¹)	RER	Power (watts)	VO ₂ (ml·kg ⁻¹ ·min ⁻¹)	VO ₂ (l·min ⁻¹)	%SaO ₂
BTPS							
1	195	170.2	1.22	490	70.7	5.2	90.2
2	190	179.3	1.21	446	68.2	5.0	89.9
3	177	199.2	1.19	435	66.4	5.3	92.3
4	187	173.8	1.16	422	72.1	4.6	89.7
5	186	206.2	1.37	461	66.2	4.6	93.7
6	169	203.3	1.30	414	62.7	4.7	94.3
7	192	215.4	1.26	505	65.7	5.1	93.9
8	192	181.1	1.29	506	57.4	5.1	92.1
9	194	198.1	1.28	455	67.1	5.0	92.4
10	185	220.7	1.22	457	71.2	5.0	91.8
Mean	186.7	194.7	1.25	459.1	66.8	5.0	92.0

Submaximal Exercise

In order to maintain VO₂ (ml·kg⁻¹·min⁻¹) at each submaximal intensity for the full 10 minutes, power (watts) was manually monitored by the researcher during each test and adjusted accordingly. By the end of each 10 minute submaximal exercise session, power values obtained from maximal exercise were decreased by an average of 24%, 15%, and 13% for each of the 90%, 60% and 30% exercise intensities. This allowed each subject to exercise

as close to the desired VO_2 ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) intensity for the full 10 minute period. Mean VO_2 ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) values averaged over the entire 10 minutes at each submaximal intensity were 89%, 61%, and 33 % respectively. The maximal values of heart rate and expired gases during each exercise intensity are shown in Table 3.

Table 3. Mean group values for submaximal exercise heart rate (HR), minute ventilation (V_E), and respiratory exchange ratio (RER).

	Exercise Intensity		
	90%	60%	30%
HR (bpm)	181.7 (7.4)	143.7 (9.5)	103.1 (5.5)
V_E ($\text{l}\cdot\text{min}^{-1}$)	180.5 (16.7)	89.2 (4.2)	49.1 (6.1)
RER	1.3 (0.1)	1.0 (0.1)	1.0 (0.1)

Values are mean ($\pm$ Std. Dev.)

Post-exercise measures of $\text{DLco}_{(21\%)}$ decreased significantly from baseline after each submaximal exercise session ($F=23.05$, $p<0.001$) (Table 4, Figure 1). $\text{DLco}_{(90\%)}$ also decreased significantly from baseline at each of the exercise intensities ($F=9.24$, $p<0.001$) (Table 4, Figure 2).

Table 4. Baseline and mean %SaO₂ during exercise and post-exercise DLco, Vc, and DM.

Dependent Variable	Baseline	90% Exercise	60% Exercise	30% Exercise
%SaO ₂	98.3 (0.3)	92.3 ^{**†} (1.5)	95.5 [*] (0.9)	96.6 [*] (0.5)
		-6.1%	-2.8%	-1.8%
DLco _(21%) (ml·min ⁻¹ ·mmHg ⁻¹)	41.1 (6.8)	34.7 [*] (6.1)	36.9 [*] (5.3)	36.6 [*] (5.9)
		-15.6%	-10.4%	-11.0%
DLco _(90%) (ml·min ⁻¹ ·mmHg ⁻¹)	20.2 (3.5)	17.5 [*] (3.1)	18.3 [*] (2.6)	18.4 [*] (3.2)
		-13.8%	-9.7%	-9.2%
Vc	114.2 (22.2)	100.6 (18.7)	106.2 (16.5)	106.3 (21.9)
		-12.0%	-7.1%	-7.0%
DM	79.8 (15.1)	64.1 [*] (12.6)	66.9 [*] (11.6)	68.5 (12.6)
		-19.7%	-16.1%	-14.1%

Values are means (± Std. Dev.). Values below means are % reduction from baseline.

* Significantly different from baseline (p<0.05), ** (p<0.01), † significantly different from 60% and 30% exercise.

The post-exercise reductions in DLco were accompanied by post-exercise declines in Vc and DM. The decline in post-exercise DM was statistically significant from baseline following the 90% (F=18.06, p<0.01) and 60% (F=15.61, p<0.01) exercise tests but did not reach significance after the 30% (F=3.91, p>0.05) exercise session (Table 4, Figure 4). The post-exercise decline in Vc failed to show a statistically significant decrease from baseline following any of the submaximal exercise sessions (F=2.28 p=0.10) (Table 4, Figure 3). The post-exercise reductions in DLco, Vc, and DM were greater after the 90% exercise session compared to the 60% and 30% sessions, but this difference did not reach statistical significance (Table 4). In addition, the post-exercise reductions in DLco_(21%) at each exercise

intensity were highly correlated with the post-exercise decline in DM (r range = 0.839 to 0.94, $p < 0.01$) and Vc (r range = 0.739 to 0.93, $p < 0.05$) (Table 5).

Table 5. Correlation Matrix for DLco_(21%) versus Vc, DM, and DLco_(90%) at each submaximal exercise intensity.

	<u>DLco_(21%)</u>			
	Baseline	Post 90%	Post 60%	Post 30%
Vc	0.81**	0.90**	0.77**	0.73*
DM	0.84**	0.94**	0.91**	0.83**
DLco _(90%)	0.95**	0.98**	0.94**	0.93**

*Significant linear relationship ($p < 0.05$), ** ($p < 0.01$).

%SaO₂ significantly decreased from baseline during exercise at each of the submaximal exercise intensities ($F = 85.06$, $p < 0.001$) (Table 4, Figure 5). The %SaO₂ reduction during 90% exercise was also significantly greater than the decline during the 60% exercise ($F = 13.59$, $p < 0.01$) and the 30% exercise ($F = 28.32$, $p < 0.01$). Individual values for the lowest achieved %SaO₂ at all exercise intensities were not correlated with the post-exercise reductions in DLco ($r = 0.33$). In addition, no correlation was found between the lowest %SaO₂ during exercise and post-exercise DLco, Vc, or DM, 1 hour following each of the submaximal exercise sessions (Table 6).

Table 6. Correlation Matrix for %SaO₂ versus DLco, DM, and Vc at each submaximal exercise intensity.

	Baseline	<u>%SaO₂</u> 90%	60%	30%
DLco_{21%} (ml·min⁻¹·mmHg⁻¹)	0.11	0.33	-0.010	-0.38
DLco_{90%} (ml·min⁻¹·mmHg⁻¹)	0.21	0.22	0.21	-0.37
DM	-0.14	0.46	-0.31	-0.28
Vc	0.26	0.11	0.36	-0.30

*Significant linear relationship (p<0.05), or ** (p<0.01).

Figure 1. Mean group pulmonary diffusing capacity (21% O₂) for carbon monoxide during rest (Baseline) and 1 hour following 90%, 60%, and 30% of maximal exercise. Percent values represent % difference from Baseline. Error bars represent standard deviation from the mean.

* Significantly different from baseline.

Figure 2. Mean group pulmonary diffusing capacity (90% O₂) for carbon monoxide during rest (Baseline) and 1 hour following 90%, 60%, and 30% of maximal exercise. Percent values represent % difference from Baseline. Error bars represent standard deviation from the mean.

* Significantly different from baseline.

Figure 3. Mean group Vc values during rest (Baseline) and 1 hour following 90%, 60%, and 30% of maximal exercise. Percent values represent % difference from Baseline. Error bars represent standard deviation from the mean.

Figure 4. Mean group DM values during rest (Baseline) and 1 hour following 90%, 60%, and 30% of maximal exercise. Percent values represent % difference from Baseline. Error bars represent standard deviation from the mean. * Significantly different from baseline.

Figure 5. Mean group arterial oxyhemoglobin values during rest (Baseline) and 1 hour following 90%, 60%, and 30% of maximal exercise. Percent values represent % difference from Baseline. Error bars represent standard deviation from the mean. ** Significantly different from baseline ($p < 0.001$); *, significantly different from baseline ($p < 0.05$); †, significantly different from 60% and 30% exercise.

DISCUSSION

This study confirms that DLco is reduced one hour following submaximal intensities of exercise. The reduction in DLco is accompanied by declines in both DM and Vc. In addition, the post-exercise decline in DLco appears to be related to the intensity of exercise but not to arterial oxyhemoglobin desaturation during exercise.

Diffusion Capacity of Carbon Monoxide in the Lung (DLco)

Baseline measures of DLco in subjects in this study are comparable to other reported studies (Turcotte et al., 1997, Rasmussen et al., 1988). The amount of decline in post-exercise DLco after maximal exercise (-10.6%) is also in agreement with other studies that measured DLco 1 hour post-exercise (McKenzie et al., 1999, Miles et al., 1983).

The present study confirms that DLco is reduced following submaximal exercise (Hanel et al., 1993, Sharratt et al., 1996). A previous study observed a 6% decrease in DLco two hours following six minutes of exercise on a rowing ergometer at 61% of maximal exercise (Hanel et al., 1993). This same study also discovered a 10% decline in post-exercise DLco two hours following 6 minutes of rowing exercise at 76% of maximal exercise. The reduction they found in DLco following 61% submaximal exercise was slightly less than the one hour post-exercise declines after 61% submaximal exercise on a cycle ergometer in the present study (-10.4%). This difference may have been a result of their use of females in their subject pool, the time of post-exercise measurement of DLco, the mode of exercise, or the duration of exercise at this intensity.

The post-exercise reduction in DLco in the present study appeared to be related to exercise intensity. The 90% submaximal exercise session produced the greatest reduction in

DLco (-15.6%) whereas the 60% and 30% exercise sessions produced similar but smaller declines (-10.4% and -10.9% respectively). However, the post-exercise reduction in DLco following 90% exercise was not significantly different from the 60% or 30% post-exercise values. These results are in agreement with those reported by Sharratt et al. (1996). For the same duration of cycling exercise, eight male university students had a 12% decrease in DLco following 75% submaximal cycling exercise which was not significantly different from a 7% decrease after both 50% and 25% submaximal exercise. Similarly, Hanel et al. (1993) found non-significant, yet greater declines in post-exercise DLco following greater intensities of exercise. The slightly greater declines in post-exercise DLco found in the present study are possibly due to the higher submaximal exercise intensities.

Further support for the relationship between exercise intensity and post-exercise DLco have been reported by Hanel et al. (1993). Although they failed to show statistical significance, they did find a greater decline in post-exercise DLco after 75% submaximal exercise compared to 61% submaximal exercise. Both of the above studies and the present study observed a greater decline in DLco following the highest intensity of submaximal exercise. Therefore, although no statistically significant results have proven this, it appears that exercise intensity plays a role on the post-exercise reduction in DLco.

A reduction in post-exercise DLco is believed to be due to a diffusion limitation secondary to pulmonary edema (Caillaud et al., 1995, Manier et al., 1991). It has been hypothesized that the decline in DLco could be inversely related to exercise intensity if pulmonary edema was present (Hanel et al., 1993). However, these authors found a decrease in post-exercise DLco after submaximal intensities of 61% and 76% and concluded that pulmonary edema would not likely be present after exercise of this intensity. The present study

supports this finding. The reduction in post-exercise DLco following 30% submaximal exercise was 10.9%. At 30% of maximal exercise cardiac output and pulmonary capillary pressure would not be elevated to a level to cause a membrane disruption and increase in interstitial fluid. Therefore, a decline in DLco at mild intensities does not support this mechanism of diffusion limitation.

An elevated carboxyhemoglobin (COHb) concentration in the blood may interrupt the diffusion of CO from the alveolar air to the pulmonary capillaries during measurement of DLco. Although COHb was not measured in this study, a previous study has reported that measurement of COHb 2 hours post-exercise does not alter DLco (Hanel et al., 1994). In addition, COHb concentrations have been found to be small and non-affective in non-smokers, and therefore, should not have affected this sample of subjects (Mohsenifar and Tashkin, 1978).

Pulmonary Membrane Diffusing Capacity (DM)

Baseline measures of DM were similar to previously reported values (Hanel et al., 1994) but higher than others reported (Sheel et al., 1998, McKenzie et al., 1999, Miles et al., 1983). The 1 hour post-exercise reductions in DM after maximal exercise are similar to other reported declines at 1 hour (McKenzie et al., 1999) and 30 minutes (Manier et al., 1993). Other studies have reported post-exercise less than the values found in this study (Rasmussen et al., 1991, Miles et al., 1983). The reason for differences between studies may only be speculated upon, but may be due to the different subject populations, different recovery periods, mode of exercise, and technique used to measure DLco.

The post-exercise reductions in DM were larger than the post-exercise declines in V_c and were greatest following the 90% submaximal exercise (-19.7%), which is also similar to the declines in DL_{co} . In addition, the post-exercise reductions in DM were inversely related to the intensity of exercise. These findings are in agreement with Sharratt et al. (1996) who also found a greater decline in DM as exercise intensity increased.

A decline in post-exercise DM has been hypothesized to represent an increase in pulmonary interstitial edema (Miles et al., 1983, Manier et al., 1991). Large increases in cardiac output during exercise may stress pulmonary capillaries to the point of capillary membrane disruption (West et al., 1991). To support this, West et al. (1991) found structural alterations in the capillary endothelial, pulmonary epithelial, and in some cases, to the basement membranes of the alveolo-capillary wall of rabbits at pressures ≥ 52.5 cmH₂O. A disruption in the alveolo-capillary membranes may allow fluid and RBCs to enter alveolar space and fill interstitial space resulting in pulmonary interstitial edema. In fact, increases in RBCs and proteins in bronchoalveolar lavage (BAL) fluid have been reported following exhaustive exercise in highly-trained subjects (Hopkins et al., 1997).

If the post-strenuous exercise reduction in DM represents pulmonary interstitial edema, as some researchers have hypothesized (Miles et al., 1983, Manier et al., 1991, Rasmussen et al., 1986, 1988), then DM would not be expected to decline following mild or moderate exercise. The present study found that DM decreased by more than 14% following 30% and 60% submaximal exercise. The same stress exerted on the pulmonary capillaries at high Q during near maximal workloads would not occur during submaximal workloads with lower Q (e.g. 60% and 30%). Although cardiac output was not measured directly in the present study, the higher HRs (Table 3) at each intensity of exercise indicates that Q was greater for each

workload. No explanation for the decline in post-exercise DM at these lower intensities can be postulated based on the data of this study. However, a recent study has suggested that the post exercise reduction in DM may, in part, be owed to the decline in Vc causing decreased capillary recruitment resulting in a reduction of the area available for gas exchange (McKenzie et al., 1999). Furthermore, they hypothesize that a decline in DM may be secondary to a hemodynamic shift of blood from the central blood volume to the periphery. This is supported by the finding that approximately 50% of the post-exercise decline in DLco is attributed to a reduction in Vc as shown by gamma camera counts of ^{99m}Tc pertechnetate labeled blood (Hanel et al., 1997). Based on this, it is possible that the present findings of a decline in DM and DLco after 60% and 30% exercise are exaggerated by reductions in Vc. However, if this is true at these submaximal intensities, it must also be true at higher intensities. Therefore, it would be very difficult to make the conclusion of a reduction in the diffusing capacity of carbon monoxide due to a diffusion limitation resulting from pulmonary edema because of the contribution of a hemodynamic shift to the decline in DM. If this is true, it would appear that the use of post-exercise measures of DLco to evaluate interstitial pulmonary edema resulting from exercise is not valid.

Pulmonary Capillary Blood Volume (Vc)

The observed decline in Vc 1 hour following maximal exercise (-7.8%) was not significant as has been shown in other reported values measured at the same time post-exercise (-11.2% and 10.1%; Sheel et al., 1998, McKenzie et al., 1999). Vc has also been shown to increase by 4% 1 hour post-exercise (Miles et al., 1983) as well as decrease by 10.2% 2 hours after exercise (Hanel et al., 1994). There is obvious variability between studies

that might be explained by differences in subject population, mode of exercise, recovery periods, or techniques used to measure DLco.

The largest reduction in Vc in this study occurred after the 90% submaximal exercise session, similar to the declines in DLco. The decline in post-exercise Vc did not reach statistical significance after any of the submaximal exercise sessions ($p = 0.10$). Reasons why results for Vc in the present study differ from previous studies (Sheel et al., 1998, McKenzie et al., 1999, Hanel et al., 1994) can only be speculated upon, but may be due to the higher variability between subjects in this study (range of Std. Dev. from 16.5 to 22.7), or for the same reasons that variability exists between other studies as stated above. A reduction in post-exercise Vc has been hypothesized to be a result of a shift of blood from the central blood volume to peripheral areas as shown by gamma camera counts of ^{99m}Tc pertechnetate labeled blood (Hanel et al., 1997).

VO₂ and %SaO₂

Maximal Exercise

The maximal values of VO₂ in subjects in the present study are similar to the values of highly trained subjects in previous studies (Martin and O'Kroy, 1993, Hopkins and McKenzie, 1989). As well, the decline in %SaO₂ observed during maximal exercise is in agreement with those reported in other studies (Dempsey et al., 1983, Hopkins and McKenzie, 1989, Sheel et al., 1998, McKenzie et al., 1999, Lawler et al., 1988). The range of %SaO₂ in the final minute of maximal exercise was 89.67 to 94.45. Three out of ten subjects had %SaO₂ levels $\leq 91\%$ which is slightly less than has been previously reported in highly-trained athletes (Powers et al., 1988). In disagreement with other studies (Williams et al., 1986, Power et al., 1988, 1989, 1993), the decline in %SaO₂ values during maximal exercise showed a moderate but non-

significant inverse relationship with VO_2max ($r = -0.56$, $p = 0.09$). However, a lack of a significant relationship between VO_2max and $\%\text{SaO}_2$ has also been observed in other studies (Turcotte et al., 1997, Harms and Stager, 1995). The reason for the lack of relationship between VO_2max and $\%\text{SaO}_2$ compared to studies that have found a relationship may be due to the small range in VO_2max values in the present study. The studies that found a relationship used a much larger range of subject fitness (untrained, moderately trained, highly trained) whereas the present study only used highly trained cyclists. The homogeneous group of subjects in the present study would not linear properties that would match those studies reported above.

Submaximal Exercise

Subjects had similar $\%\text{SaO}_2$ values following the maximal exercise session and the 90% submaximal exercise test (92.03 vs. 92.30%), and both were significantly below baseline. $\%\text{SaO}_2$ also decreased below baseline during the 60% and 30% submaximal exercise sessions but not to levels that have been found to affect performance (Koskolou and McKenzie, 1994). Similar declines in $\%\text{SaO}_2$ at submaximal intensities of 60% and 90% have been reported (Turcotte et al., 1997).

Relationship Between %SaO₂, DLco, DM, and Vc

As stated previously, the post-exercise reduction in DLco was attributed to a decline in both Vc and DM. A significant correlation was found between DLco and Vc (r range = 0.73 to 0.93, $p < 0.05$) and between DLco and DM (r range = 0.83 to 0.94, $p < 0.01$).

However, the post-exercise reduction in DLco, Vc, and DM, were not related to the decline in %SaO₂ during exercise at any of the intensities in these highly-trained athletes. Only one other study has measured %SaO₂ and DLco at different intensities of exercise (Turcotte et al., 1997). These authors compared 90% and 60% submaximal DLco during exercise in a group of non-desaturators and a group of desaturators and found no relationship between DLco and %SaO₂. Other studies support a lack of relationship between post-exercise DLco and %SaO₂. Sheel et al. (1998) found that subjects of varied fitness levels had similar reductions in DLco but only the highly-trained group experienced EIH (Sheel et al., 1998). Similarly, a second bout of exercise that resulted in a further decline in DLco was not accompanied by a further reduction in %SaO₂ (McKenzie et al., 1999). The present study, along with the work of others, support the finding that a reduction in %SaO₂ during exercise is not related to the post-exercise decline in DLco. Therefore, it appears that the use of post-exercise measurement of DLco is not a valid device for evaluation of the mechanisms of EIH.

Conclusion

The results of this study support that reductions in post-exercise DLco are related to exercise intensity. However, because of the decline in DLco and DM following submaximal exercise (30 to 60%), it appears that the evaluation of exercise-induced pulmonary edema using the measurement of post-exercise DLco is not valid. Furthermore, post-exercise changes in DLco are not related to %SaO₂ during exercise. Therefore, it appears that the post-exercise

measures of DLco do not reflect EIH, and have a questionable role in evaluating the mechanisms of this phenomenon.

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APPENDIX A
REVIEW OF LITERATURE
EXERCISE-INDUCED HYPOXEMIA

Maximal Exercise and Performance

In 1986, Dempsey reported that the ability of highly trained aerobic athletes to attain maximal performance may be inhibited by the pulmonary system's ability to maintain blood-gas homeostasis. This was the first paper to suggest that the pulmonary system may be a contributing limitation to exercise performance. Since that paper, it has been established that approximately 50% of highly-trained athletes experience a decline in arterial oxyhemoglobin saturation below 91% (Powers et al., 1988) and a reduction in the arterial pressure of oxygen 5% below resting values (Powers et al., 1992). This is known as exercise-induced hypoxemia (EIH). Reductions in arterial O₂ of this magnitude have been shown to inhibit maximal attainment of VO₂max (Powers et al., 1989) and exercise performance (Koskolou and McKenzie, 1994).

The mechanism of EIH has been studied vigorously. Possible contributors are: veno-arterial shunt, ventilation-perfusion inequality, hypoventilation, and a diffusion limitation secondary to decreased transit time or pulmonary edema.

One of the methods that has been used to evaluate an exercise-induced diffusion limitation secondary to pulmonary edema is the diffusion of carbon monoxide in the lung (DLco) (Manier et al., 1991, Miles et al., 1983, Caillaud et al., 1995). DLco has been found to increase during exercise (Turcotte et al., 1997). The expected response of DLco post-exercise would be a return to baseline levels similarly to cardiac output. However, post-exercise declines in DLco have been found to drop below baseline measures and many authors believe

that this further reduction is owed to an increase in pulmonary edema during exercise (Manier et al., 1991, Miles et al., 1983, Caillaud et al., 1995, Rasmussen et al., 1986, 1988). If this is true, then measurement of post-exercise DLco may be a valuable tool for the evaluation of pulmonary edema and EIH.

Veno-Arterial Shunt

Veno-arterial shunt is defined as the addition of poorly oxygenated mixed venous blood into arterial blood without being perfused by oxygen rich alveolar air. A significant addition of mixed venous blood into arterial blood may decrease PaO_2 and be a potential cause of EIH (Powers et al., 1993). If veno-arterial shunt was even partially responsible for EIH, increasing the alveolar pressure of O_2 (P_{AO_2}) would have no effect on the arterial pressure of O_2 (PaO_2) because mixed venous blood would still enter arterial blood. However, PaO_2 has been shown to increase with increases in P_{AO_2} and therefore, it appears that veno-arterial shunt does not contribute significantly to the cause of EIH (Dempsey et al., 1984).

Hypoventilation

A relative hypoventilatory response during heavy exercise has been suggested as a mechanism of EIH. This is defined as a blunted alveolar ventilatory (P_{AO_2}) increase as exercise intensity increases towards maximal levels which may result in a decrease in arterial PO_2 (Dempsey et al., 1984). Dempsey et al. (1984) found that when some highly trained athletes approach maximal levels of exercise, metabolic acidosis increases as well as the level of hypoxemia without a compensatory increase in the ventilatory response. They have proposed that a lack of chemoresponsiveness or a mechanical resistance or a combination of

the two to explain a lack of adequate hyperventilation of highly trained athletes exercising at high intensities (Dempsey et al., 1984, 1986).

It has been hypothesized that there may be inter-individual differences in ventilatory drive chemosensitivity causing some individuals to have blunted hyperventilation during high intensity exercise (Dempsey, 1986, Harms and Stager, 1995). Blunted increases of V_E and decreases in $PaCO_2$ have been found, even though lactate, catecholamines, and hypoxemia all increase as exercise intensity increases to maximal levels (Dempsey et al., 1984). This may characterize a decrease in the ability to detect chemical stimuli to increased ventilation (Dempsey, 1986). In support of this finding, it has been observed that a group of athletes who had a reduced hyperventilatory response to exercise also had the lowest % SaO_2 values (Harms and Stager, 1995). Furthermore, these athletes had positive relationships between the hypoxic ventilatory response (HVR) and hypercapnic ventilatory response (HCVR) at rest and SaO_2 during maximal exercise. This indicates that these athletes had a low hypoxic and hypercapnic drive to exercise. In contrast to this finding, no relationships were observed between resting HVR and ventilation measures during exercise or resting HVR and % SaO_2 during exercise (Hopkins and McKenzie, 1989). Therefore, the level of chemoresponsiveness may explain some of the inadequate hyperventilation during maximal exercise, but further study needs to address this possibility.

A mechanical limitation may also contribute to a lack of hyperventilation during heavy exercise. It has been proposed that athletes that work at very high levels (VCO_2 of 5 - 6 $l \cdot min^{-1}$) do not achieve a V_E (200 $l \cdot min^{-1}$) to support the increased ventilatory demand created (Dempsey 1986). Support of this is evident in that breathing a lower density gas such as helium ($He:O_2$) immediately results in an increased ventilation (Dempsey 1984, Dempsey

and Fregosi, 1985). In addition, it has been shown that more work is required to produce a voluntary near maximum flow rate as opposed to an involuntary near maximum flow rate as seen by increased pressure:volume ratios during voluntary maximal breathing (Dempsey, 1986). This author also proposed that there may be feedback inhibition from the chest wall to the brain stem that decreases the respiratory drive at high intensity exercise which may be a protective mechanism against respiratory muscle fatigue. Therefore, combination of chemical and mechanical limitations may result in a decreased hyperventilatory response which may result in a decreased P_{AO_2} and EIH.

Further support for a lack of hyperventilatory response at near-maximal and maximal exercise has been found in a group of moderate to highly trained athletes ($VO_{2max} = 60.9 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) who desaturate (88.2%) as determined by finger oximetry (Turcotte et al., 1997). These athletes had lower V_E/VO_{2max} levels compared to a second group of moderate to highly trained ($VO_{2max} = 57.7 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) non-desaturators (92.9%) (Turcotte et al., 1997). In addition, a second study found that highly trained athletes do not have the same hyperventilatory response to maximal exercise as untrained athletes (Caillaud et al., 1993). The highly trained athletes ($VO_2 = 68.6 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) had lower P_{AO_2} levels, lower V_E/VO_{2max} levels, elevated $PaCO_2$ levels, coupled with a hypoxemic response during exercise compared to the untrained ($VO_2 = 46.3 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) athletes (Caillaud et al., 1993).

A recent study has observed the relationship between % SaO_2 and ventilation during maximal exercise at normal O_2 (20.9% O_2) pressures and at hypoxic pressures (13.3% O_2) (Gavin et al., 1998). Subjects were divided into groups based on their ventilatory response to maximal exercise at normal O_2 pressures. The low ventilatory group during normoxic exercise had a greater hypoxic arterial desaturation and also a greater decline in VO_{2max} during

hypoxic exercise. These results support that a lack of hyperventilatory response during normoxic exercise reduces %SaO₂ during hypoxic exercise compared to a group of athletes that have a normal ventilatory response to exercise. However, the group with a blunted hyperventilatory response did not have lower %SaO₂ values during normoxic exercise, and therefore, the results of this study do not address the contribution of this mechanism during normoxic exercise. Although this evidence indicates further support for a hypoventilatory response to maximal exercise in highly trained athletes, the exact contribution is unknown.

There is, however, evidence that does not support hypoventilation as a cause of EIH. It has been reported that there is a large inter-individual variation of the hyperventilatory response to high-intensity exercise and this is unrelated to V_E/VO_2 , V_E alone, or arterial hypoxemia (Hopkins and McKenzie, 1989). This contradicts results found by Turcotte et al. (1997). In addition, it has been found that less than 27% of the variance between P_AO_2 and PaO_2 can be explained at workloads of 90% of maximal or greater (Powers et al., 1992). Finally, although V_E , V_E/VO_2 , and V_E/VCO_2 all increase when breathing a heliox (21% O₂, 79% He) gas mixture compared to ambient air, no change is found in arterial oxyhemoglobin saturation between tests (Buono and Maly, 1996). There appears to be no relationship between the alveolar pressure of O₂ and the arterial pressure of O₂ based on the findings from Hopkins and McKenzie (1989), Powers et al. (1992), or Buono and Maly (1996).

In summary, although a lack of adequate hyperventilation has been stated to account for approximately 50% of the variability in %SaO₂ (Harms and Stager, 1995), other studies have not observed a relationship between ventilation and EIH (Hopkins and McKenzie, 1989, Powers et al., 1989, Buono and Maly, 1996). Therefore, it appears that a lack of

hyperventilation may contribute to EIH during exercise, but the amount of this contribution remains inconclusive.

Ventilation-Perfusion Inequality

Ventilation-perfusion (VA/Q) inequality is defined as a mismatch between pulmonary ventilation and blood flow that may result in the alteration of O₂ and/or CO₂ concentration gradients across the blood-gas barrier (West et al., 1990). An alteration in VA/Q has been hypothesized to contribute to a reduction of end arterial PO₂ (PaO₂) and/or oxyhemoglobin %SaO₂ (Wagner et al., 1986). Multiple inert gas elimination analysis of retention and excretion of gases permits an indirect evaluation of VA/Q inequality. Studies at simulated altitude and sea level have used a model that predicts the alveolar to arterial O₂ difference (A-aDO₂) which can be used to compare the observed values of the alveolar to arterial difference in oxygen (A-aDO₂). This predicted value of A-aDO₂ represents VA/Q inequality and intrapulmonary shunt while the difference between the predicted and observed A-aDO₂ values represents a combination of diffusion limitation and post-pulmonary shunt (Gale et al., 1985, Hopkins et al., 1994). Post-pulmonary shunt has been excluded as a cause of VA/Q inequality because breathing 100% O₂ during exercise restores the A-aDO₂ to resting levels (Wagner et al., 1986).

It was previously believed that VA/Q inequality was not evident at sea level (Torre-Bueno et al., 1985). However, studies in which subjects exercise at intensities $> 3.0 \text{ l} \cdot \text{min}^{-1}$ have resulted in an increase in VA/Q inequality (Hammond et al., 1986). In fact, the total A-aDO₂ has been shown to be greater than predicted levels which indicates a diffusion limitation at sea level (Wagner et al., 1986). The mechanism of this is speculated as an increase in

pulmonary edema, hypoxic ventilatory vasoconstriction, or a ventilatory time constant inequality (Hammond et al., 1986, Wagner et al., 1986). These are hypothesized because of the high correlations between mean pulmonary arterial pressures versus VA/Q inequality and ventilation. Wagner et al. (1986) found that during exercise at sea level, two-thirds of the total A-aDO₂ is due to a diffusion limitation and the remaining one third is due to VA/Q alone. These results are similar to results found at altitude (Gale et al., 1985). Therefore, in theory, even higher intensities ($\text{VO}_2 > 5 \text{ l}\cdot\text{min}^{-1}$) should increase the distance between the observed and predicted A-aDO₂ values and, hence, result in even more contribution of a diffusion limitation to the total A-aDO₂. However, highly trained athletes that exercised at a mean VO_2 of $5.15 \text{ l}\cdot\text{min}^{-1}$ at sea level did increase VA/Q inequality which accounted for greater than 60% of the total A-aDO₂ (Hopkins et al., 1994). Upon examination, Hopkins et al. (1994) concluded that the VA/Q mismatch was due to an increase in blood flow to the areas of high VA/Q rather than a shunting effect or low VA/Q areas.

Further evaluation of VA/Q inequality has led to increased support for the role of diffusion limitation. A functional mechanism of EIH such as VA/Q inequality would be expected to decrease after exercise in direct relation to the decline in cardiac output and expired volume. However, a structural abnormality resulting in pulmonary edema may last further into recovery. To test this directly, Schaffartzik et al. (1992) performed a study in which subjects breathed a hypoxic gas mixture containing 12.9 % O₂ (91 Torr). One group had a VA/Q inequality greater than 10% during exercise while the second group did not. The group with the elevated VA/Q inequality during exercise also remained elevated 20 minutes into recovery whereas the second group reduced VA/Q inequality down to baseline levels (Schaffartzik et al., 1992). From this, it was concluded that cardiac output and ventilation

measures in post-exercise could not account for the VA/Q inequality and therefore pulmonary edema must have been present in these subjects. Similar results to this study have also been reported (Hammond et al., 1986, Wagner et al., 1986). This indicates that a structural alteration must be present or the VA/Q inequality would decrease as cardiac output and ventilation returned to baseline levels.

In summary, most studies have found that a diffusion limitation may contribute to the A-aDO₂ during exercise more than VA/Q inequality. However, the results by Hopkins et al. (1994) lend controversy as to the contribution of VA/Q inequality during high-intensity exercise in elite athletes.

Diffusion Limitation Pulmonary Capillary Transit Time

Pulmonary capillary transit time (TT) is the time period that a red blood cell (RBC) is exposed to the blood gas barrier where O₂ diffuses down a concentration gradient from the alveoli into blood from the right side of the heart. Through morphological studies to determine capillary capacities, it has been hypothesized that the capillary blood volume (V_c) reaches its limits at approximately 220 ml at a cardiac output (Q) of approximately 25 l·min⁻¹ (Dempsey and Fregosi, 1985). At Q of 25 l·min⁻¹ the TT of RBCs passing through the pulmonary capillaries is approximately 0.35 to 0.40 seconds, which is believed to be adequate for full saturation of O₂. In highly trained athletes, VO₂ values may reach 4.0 - 5.0+ l·min⁻¹ which would require Q values to exceed 25 l·min⁻¹ and therefore reduce the amount of TT below 0.35 seconds (Dempsey et al., 1984). From this, it could be assumed that in highly trained athletes working at maximal intensities, V_c would be expected to plateau at 220 ml as Q continued to increase. To test this, a group of highly trained athletes (VO₂max = 4.9

$\text{l}\cdot\text{min}^{-1}$) exercised on a cycle ergometer at work outputs reaching 88% of VO_2max (Warren et al., 1991). Mean Q values reached $29.4 \text{ l}\cdot\text{min}^{-1}$ at 88% of maximal VO_2 (mean $\text{VO}_2 = 4.31 \text{ l}\cdot\text{min}^{-1}$), but Vc did not plateau and TT remained unchanged even at these higher workloads (Warren et al., 1991). It was concluded that TT was not a factor in a diffusion limitation or a cause of EIH.

However, in a separate study, highly trained athletes ($\text{VO}_2\text{max} = 5.15 \text{ l}\cdot\text{min}^{-1}$) exercised at >90% of maximal VO_2 (mean $\text{VO}_2 = 5.13 \text{ l}\cdot\text{min}^{-1}$) on a cycle ergometer (Hopkins et al., 1996). At these work outputs, Q values reached $33 \text{ l}\cdot\text{min}^{-1}$ and whole lung TT decreased from 9.32 to 2.91 seconds. The estimated pulmonary capillary TT was 0.39 to 0.41 seconds which is higher than what is believed to cause a diffusion limitation (< 0.35 seconds). However, the frequency distribution of whole lung TT was used to estimate that over 40% of the pulmonary capillary TT was less than 0.30 seconds and 15% of the pulmonary capillary TT was less than 0.14 seconds (Hopkins et al., 1996). These values are much lower than the value of 0.35 seconds that is the acceptable value for a diffusion limitation (Dempsey, 1986). In addition, it is believed that the intensities reached during the Warren et al. (1991) study were not high enough to elicit a plateau in Vc and an eventual decrease in TT (Hopkins et al., 1996). Therefore, it may be concluded that TTs in highly trained athletes working at high work outputs could inhibit O_2 saturation of arterial blood. The exact contribution of TT to the cause of EIH is not known.

Diffusion Limitation Pulmonary Edema

An increase in extravascular water caused by high pulmonary capillary pressures during high intensity exercise theoretically may increase the diffusion distance of gas across

the blood-gas barrier. This may result in a reduced pulmonary end-capillary O_2 pressure or a decrease in the arterial oxyhemoglobin saturation of O_2 (%Sa O_2).

Indirect assessment of diffusion limitation during exercise has led a number of researchers to believe that pulmonary edema may be a cause of EIH. Buono et al. (1983) found that thoracic electrical impedance (TEI) decreases after graded treadmill exercise to exhaustion and is accompanied by an increase in residual volume (RV). They concluded that increased capillary hydrostatic pressure and surface area during exercise increases extravascular fluid accumulation in the peribronchial interstitial space. This may decrease the small airway diameter forcing peripheral airways to close earlier upon expiration which could trap more air resulting in increased RV after exercise. In support, a second study found that pulmonary vascular resistance may be altered by an increase in intravascular water in the peribronchial or perivascular interstitium and therefore affect the distribution of blood flow and/or ventilation resulting in VA/Q inequality at VO_2 levels $> 3.0 \text{ l} \cdot \text{min}^{-1}$ (Hammond et al., 1986, Wagner et al., 1986). As stated previously, it has also been found that VA/Q inequality persists into recovery of exercise which cannot be explained by a return of ventilation and cardiac output values to baseline levels, suggesting a structural alteration and pulmonary edema (Schaffartzik et al., 1992). Furthermore, it has been found that lymph flow during exercise increases in relation to increases in cardiac output so that the filtration pressure may exceed the threshold for edema formation (Younes et al., 1987). Although all of the above indirect assessments may indicate pulmonary edema, it does not provide concrete evidence for a diffusion limitation.

In an attempt to directly evaluate pulmonary edema post-exercise, more recent studies have uncovered further evidence of pulmonary edema occurring as a result of increased

pulmonary hydrostatic pressures. The thorax of eight male athletes were CT-scanned before and after a triathlon race (Caillaud et al., 1995). Although there were no obvious images of interstitial or alveolar pulmonary edema, the authors did observe evidence of an increase in post exercise lung density and linear and polygonal opacities indicating an increase in extravascular water (Caillaud et al., 1995). However, these authors noted that the increased pulmonary density may have been due to higher pulmonary blood flow post-exercise and that changes might not be visible using this technique because of the small amounts of water involved.

In order to evaluate the blood-gas barrier and possible alterations resulting in pulmonary edema during high intensity exercise, bronchoalveolar lavage (BAL) fluid assessment was performed on highly trained athletes after 4.0 km of uphill cycling (Hopkins et al., 1997). They observed a post-exercise increase in red blood cells, alveolar macrophages, and proteins such as albumin and LTB_4 into the alveolar spaces (Hopkins et al., 1997). It was concluded that the exercise performed increased the pulmonary capillary pressure enough to alter the blood-gas barrier and therefore allowed an increase in the permeability of red blood cells (RBCs) and proteins into alveolar spaces. To support this finding, direct electron microscope analysis of rabbit lungs at high pulmonary pressures have revealed erythrocytes entering the alveolar spaces (West et al., 1991).

Two studies report direct assessment of pulmonary capillary membrane integrity at high pressures in rabbits (West et al., 1991, Tsukimoto et al., 1991). It was observed that capillary endothelial and pulmonary epithelial membrane disruptions occurred at pressures equal to and above 52.5 cmH₂O and this was accompanied by a disruption of the basement membrane 50% of the time (Tsukimoto et al., 1991). In addition, the thickness of the blood-

gas wall increased at pressures equal to and greater than 32.5 cmH₂O, and this was believed to be caused by an increase of water into the interstitial spaces (Tsukimoto et al., 1991). Therefore, it appears that speculation made by some researchers may have some concrete evidence of membrane disruption in an animal model caused by high pulmonary capillary pressure leading to an increase in interstitial pulmonary edema.

Pulmonary Diffusion Capacity

Measurement of the diffusion capacity of carbon monoxide in the lung (DLco) has been used to indirectly evaluate diffusion limitations of the pulmonary system. It has also been used as an assessment tool to evaluate a diffusion limitation as a cause of EIH (Hanel et al., 1994, Manier et al., 1991). By using two concentrations of gas, DLco can be partitioned into two components: the diffusing capacity of the alveolar membrane (DM), and the rate of the gas uptake by the blood which is represented by the rate of gas combining with hemoglobin within the red blood cell (θ) and pulmonary capillary blood volume (Vc). Variables that contribute to changes in DM are the membrane surface area and membrane thickness for the transfer of gases, whereas changes in Vc are affected by the number of pulmonary capillaries recruited and the distension of flowing capillaries (Johnson et al., 1960).

DLco increases with exercise due to increases in both DM and Vc (Johnson et al., 1960). DLco has also been shown to decrease post-exercise with the greatest decline occurring at approximately 6 hours and recovery approaching baseline at 24 hours (Sheel et al., 1998). Controversy exists as to the cause of the decline in DLco post exercise.

DM only has been shown to decline 30 minutes, 1 hour, and 24 hours after a marathon (Miles et al., 1983, Manier et al., 1991) as well as 30 minutes after a 20 minute bout of

ramped, maximal cycling exercise (Manier et al., 1993). DM has also been shown to decrease in conjunction with Vc after cycling to fatigue exercise (Sheel et al., 1998) and after a ramped cycling to exhaustion protocol (McKenzie et al., 1998). A decline post-exercise DM has been hypothesized to indicate an increase in pulmonary interstitial edema which may increase the diffusion distance of alveolar gases across the alveolo-capillary membrane (Miles et al., 1983, Manier et al., 1991). This persistent accumulation of fluid is likely a result of increased capillary pressures which could alter the capillary endothelial and/or alveolar epithelial membrane integrity (West et al., 1991). Furthermore, according to Starling, pulmonary edema may result from elevated capillary hydrostatic pressure, increased capillary permeability to plasma proteins, increased capillary surface area, and decreased lymphatic drainage. Similarly, an increase in intrathoracic fluid accompanied by no change in DLco despite an increase in post exercise heart rate (HR) lends indirect support to an increase in post-exercise pulmonary edema (Buono et al., 1983).

Vc has also been shown to progressively decrease to 6 hours post-exercise followed by a gradual increase to baseline levels by 24 hours (Sheel et al., 1998). This decrease in post-exercise Vc has been hypothesized to reflect a shift of blood flow from the thoracic region to peripheral areas of the body (Hanel et al., 1997). This is evidenced by measuring the distribution of technetium-99m (^{99m}Tc) labeled erythrocytes on a gamma camera. Using this method, a decrease in central fluid and an increase in fluid to the thigh has been found to occur 2.5 hours after 6 minutes of maximal rowing (Hanel et al., 1997). It was concluded that approximately 50% of the reduction in DLco was explained by the movement of fluid from the central volume to the periphery.

A second method of evaluating the shift of blood flow is by thoracic electrical impedance (TEI). A decline in TEI indicates an increase in fluid to the thoracic region and vice versa. TEI has been shown to increase 2.4 hours after arm cranking, treadmill running, and ergometer rowing, and was accompanied by a decline in post-exercise DLco (Rasmussen et al., 1992). Further support for a dominant role of Vc for the decline in DLco has been shown in a study from our lab where a repeat bout of maximal exercise following an initial maximal bout found a post-exercise decrease in DLco and Vc but not DM (McKenzie et al., 1998).

Diffusion Capacity (DL) and EIH

Recent studies have indirectly raised the question whether the measurement of DLco reflects the changes in arterial O₂ saturation levels of athletes during exercise. It would be expected that after an initial maximal exercise session that produced a decline in DLco and %SaO₂, a repeated bout of maximal exercise would produce a further decline in DLco and arterial O₂ saturation levels. However, although DLco decreased further, the repeated bout of maximal cycling did not reduce the level of arterial O₂ desaturation beyond those observed after the first bout of exercise (McKenzie et al., 1999). Furthermore, it would be expected that as approximately 50% of elite athletes show signs of desaturation (Powers et al., 1988), only these athletes would show a decline in DLco following exercise. This is assuming that one of the mechanisms of EIH is pulmonary edema and that a decrease in DLco accompanied by a decline in DM reflects this. However, it has been found that highly trained, moderately trained, and untrained subjects have the same decline in post-exercise DLco regardless of %SaO₂ status during exercise (Sheel et al., 1998).

DLco, EIH, and Intensity of Exercise

During exercise at intensities greater than 80% of maximal values, arterial oxygen levels decline to a point that may affect performance or maximal VO_2 values (Koskolou and McKenzie, 1994). At these higher intensities, pulmonary capillary pressures have been found to be in excess of 40 mmHg (Moon et al., 1984). Therefore, it could be hypothesized that post-exercise reductions in DLco at high intensities could be greater than those after less intense exercise. Also, this decline could be attributed to the membrane component (DM) of the decrease in DLco due to an increase in pulmonary interstitial edema caused by the high capillary pressures. In fact, a strong inverse relationship would be expected to be present between exercise intensity and the post-exercise measures of DLco and DM. Two studies have measured post-exercise DLco at different intensities. Hanel et al. (1994) did not find a relationship between the post-exercise decline in DLco and intensity at 61% and 76% of $\text{VO}_{2\text{max}}$. However, they did state that if the post-exercise decline in DLco was included after the maximal exercise session, a trend of greater declines in DLco at higher intensities of exercise did occur. They did not, however, report on the effects of DM and V_c at these various intensities. In a second study, Sharratt et al. (1996) found significant reductions in post-exercise DLco at exercise intensities of 75%, 50%, and 25% of maximal VO_2 . These authors stated that post-exercise DLco decreased twice as much following the 75% exercise when compared to the 50% and 25% intensities. By partitioning DLco, they also found that DM declined progressively more as exercise intensity increased while V_c showed a main effect for time. These authors did not measure arterial O_2 levels and therefore no relationship

between post-exercise DLco and %SaO₂ after exercise of various intensities have been reported.

One other study has measured DLco during exercise has measured %SaO₂ and DLco during exercise in a group of non-desaturators and desaturators (Turcotte et al., 1997). They found no difference in DLco between groups even though one of the groups desaturated.

In summary, it appears that post-exercise declines in DLco are due to a reduction in Vc and DM. However, the contribution of each of these components is controversial. Furthermore, although DLco measures the diffusion capacity of the lung, its relevance as a tool to examine the mechanisms of EIH is questionable.

Conclusion

Despite exhaustive efforts, the mechanism of EIH remains controversial. Veno-arterial shunt has been ruled out as a possible contributor. Therefore, it appears that the mechanism of EIH is attributed to some combination of VA/Q inequality, hypoventilation, and diffusion limitation as a result of a reduced transit time or pulmonary edema. The exact contribution of each as the mechanism of EIH cannot be determined based on the research thus far. However, the measurement of post-exercise DLco does not appear to be related to EIH and therefore should not be used as a tool for evaluation.

APPENDIX B

RAW DATA

Table 7. Age, height, and mass, individual subject data.

Subject	Age (yrs)	Height (cm)	Mass (Kg)
1	20	181.3	73.3
2	25	181.9	73.2
3	32	175.7	81.2
4	30	172.7	64.2
5	23	178.2	69.4
6	35	182.5	75.3
7	20	185.8	76.7
8	32	194.6	85.1
9	27	178.9	73.0
10	31	180.4	69.7

Table 8. Pulmonary function, individual subject data.

Subject	FVC (L)	FEV ₁ (L)	FEV ₁ /FVC (%)	FEF _{25-75%} (L·sec ⁻¹)
1	6.15	5.22	84.88	5.53
2	5.96	4.87	81.81	4.93
3	5.14	4.25	82.68	4.56
4	4.95	3.88	78.38	3.99
5	5.54	4.94	89.20	8.54
6	5.89	4.98	84.55	5.27
7	6.22	5.38	86.50	5.91
8	6.77	5.47	80.80	9.15
9	5.21	4.44	85.22	4.72
10	5.31	4.65	87.57	5.57

Table 9. Pulmonary diffusion capacity (21% O₂) pre and one hour post-exercise at each intensity, individual subject data.

Subject	DLco (pre) (ml·min ⁻¹ ·mmHg ⁻¹)	DLco 100% (ml·min ⁻¹ ·mmHg ⁻¹)	DLco 90% (ml·min ⁻¹ ·mmHg ⁻¹)	DLco 60% (ml·min ⁻¹ ·mmHg ⁻¹)	DLco 30% (ml·min ⁻¹ ·mmHg ⁻¹)
1	42.87	38.74	40.60	42.01	42.7
2	33.9	30.95	31.33	31.93	34.46
3	42.22	39.33	35.04	36.34	35.58
4	36.72	30.06	29.26	33.42	30.17
5	38.13	36.13	31.36	33.60	34.4
6	40.75	34.84	29.26	36.42	34.10
7	52.64	49.63	47.67	45.74	46.79
8	52.09	46.93	39.90	44.08	44.40
9	39.39	31.34	32.50	34.21	33.73
10	32.68	29.86	30.00	30.86	29.81

Table 10. Pulmonary diffusion capacity (90% O₂), pre and one hour post-exercise at each intensity, individual subject data.

Subject	DLco pre (ml·min ⁻¹ ·mmHg ⁻¹)	DLco 100% (ml·min ⁻¹ ·mmHg ⁻¹)	DLco 90% (ml·min ⁻¹ ·mmHg ⁻¹)	DLco 60% (ml·min ⁻¹ ·mmHg ⁻¹)	DLco 30% (ml·min ⁻¹ ·mmHg ⁻¹)
1	21.61	19.30	21.59	21.01	21.09
2	18.68	15.64	15.99	15.44	15.67
3	19.26	18.24	17.10	18.21	16.81
4	17.80	15.74	15.39	18.53	16.71
5	17.91	17.75	15.78	16.96	16.87
6	20.77	17.33	13.66	18.34	18.55
7	26.70	25.47	23.10	22.94	22.87
8	25.57	23.60	20.04	20.30	24.02
9	17.76	14.97	16.73	16.21	16.70
10	16.23	14.67	15.07	14.74	14.32

Table 11. Membrane diffusing capacity, pre and one hour post-exercise at each intensity, individual subject data.

Subject	DM pre	DM 100%	DM 90%	DM 60%	DM 30%
1	78.4	66.6	68.2	74.5	80.9
2	54.3	55.2	56.1	58.7	76.4
3	94.1	84.6	67.9	67.3	72.9
4	72.2	51.9	50.0	51.5	48.0
5	79.7	69.2	57.7	58.5	65.9
6	73.2	65.2	61.5	64.0	55.6
7	95.4	88.3	93.7	80.6	89.9
8	99.9	86.1	73.2	89.6	72.8
9	89.5	63.0	57.2	65.9	63.5
10	61.1	56.7	55.0	58.7	59.2

Table 12. Pulmonary capillary blood volume, pre and one hour post-exercise at each intensity, individual subject data.

Subject	Vc pre	Vc 100%	Vc 90%	Vc 60%	Vc 30%
1	125.2	122.5	132.4	122.9	118.4
2	119.2	92.9	93.8	87.4	83.5
3	100.3	96.4	95.3	105.9	92.3
4	98.1	93.9	92.7	121.2	106.8
5	96.2	99.4	90.3	100.1	94.7
6	121.5	98.9	73.2	107.3	116.4
7	154.5	149.2	127.7	133.3	128.5
8	143.3	135.8	114.5	110.2	149.1
9	92.0	81.5	99.2	90.6	94.1
10	92.1	83.4	86.5	82.8	78.8

Table 13. Arterial oxyhemoglobin saturation before and during exercise at each intensity, individual subject data.

Subject	%SaO₂ pre	%SaO₂ 100%	%SaO₂ 90%	%SaO₂ 60%	%SaO₂ 30%
1	98.2	91.2	92.0	95.7	96.0
2	98.1	89.9	93.0	96.0	96.9
3	97.9	92.3	90.1	95.2	96.7
4	98.1	89.7	90.1	96.0	97.3
5	98.2	93.7	92.0	95.7	97.0
6	98.6	94.3	94.4	96.3	96.7
7	98.5	93.9	94.5	96.1	96.7
8	98.6	92.1	92.4	94.3	95.9
9	98.1	92.4	93.0	95.3	96.2
10	98.9	91.8	91.8	93.9	96.1

Table 14. Maximal power (observed) and mean power (observed) during the last minute of each submaximal exercise session, individual subject data.

Subject	Power 100% (watts)	Power 90% (watts)	Power 60% (watts)	Power 30% (watts)
1	490	320	230	129
2	446	335	235	120
3	435	325	230	110
4	422	300	215	105
5	461	285	220	119
6	414	305	225	111
7	505	325	250	129
8	506	331	248	134
9	455	300	247	120
10	457	300	235	125

Table 15. Maximal oxygen consumption ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) during maximal and submaximal exercise, individual subject data.

Subject	VO ₂ max ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	VO ₂ 90% ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	VO ₂ 60% ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	VO ₂ 30% ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)
1	70.7	62.1	43.5	29.5
2	68.2	60.1	41.6	22.7
3	66.4	58.7	40.1	21.7
4	72.1	63.5	42.1	21.5
5	66.2	60.6	40.7	20.7
6	62.7	56.9	37.7	21.6
7	65.7	59.6	42.3	22.1
8	57.4	51.3	36.4	19.2
9	67.1	58.2	40.6	21.1
10	71.2	60.1	42.6	22.4

Table 16. Maximal oxygen consumption ($\text{l}\cdot\text{min}^{-1}$) during maximal and submaximal exercise, individual subject data.

Subject	VO ₂ max ($\text{l}\cdot\text{min}^{-1}$)	VO ₂ 90% ($\text{l}\cdot\text{min}^{-1}$)	VO ₂ 60% ($\text{l}\cdot\text{min}^{-1}$)	VO ₂ 30% ($\text{l}\cdot\text{min}^{-1}$)
1	5.2	4.5	3.1	2.2
2	5.0	4.4	3.1	1.7
3	5.3	4.7	3.2	1.7
4	4.6	4.0	2.8	1.3
5	4.6	4.2	2.8	1.4
6	4.7	4.5	2.9	1.7
7	5.1	4.6	3.2	1.7
8	5.1	4.4	3.3	1.7
9	5.0	4.1	2.9	1.5
10	5.0	4.2	3.0	1.6

Table 17. Peak heart rate during maximal and submaximal exercise, individual subject data.

Subject	HR 100%	HR 90%	HR 60%	HR 30%
1	195	188	149	111
2	190	188	146	107
3	177	186	145	105
4	187	186	143	104
5	186	182	140	100
6	169	165	119	92
7	192	185	149	102
8	192	174	148	101
9	194	185	154	108
10	185	178	144	100

Table 18. Peak minute ventilation during maximal and submaximal exercise, individual subject data.

Subject	V _E 100%	V _E 90%	V _E 60%	V _E 30%
1	170.2	163.9	89.3	59.3
2	179.3	167.7	83.8	47.3
3	199.2	195.4	91.4	47.2
4	173.8	162.4	87.2	49.8
5	206.2	174.2	91.1	45.2
6	203.3	182.7	91.0	58.3
7	215.4	204.3	98.6	48.5
8	181.8	162.3	85.3	51.2
9	198.1	188.9	86.3	40.1
10	220.7	202.8	87.8	42.7

APPENDIX C
STATISTICAL ANALYSIS

Table 19. ANOVA table for DLco 21% O₂

Source of Variance	df	Sum of Squares	Mean Square	F-Ratio	P-Value
Between groups	3	222.001	74.000	23.047	<0.0001
Error (within groups)	27	86.691	3.211		
Total	30	308.692			

Table 20. ANOVA table for DLco 90% O₂

Source of Variance	df	Sum of Squares	Mean Square	F-Ratio	P-Value
Between groups	3	41.527	13.842	9.244	<0.0001
Error (within groups)	27	40.431	1.497		
Total	30	80.958			

Table 21. ANOVA table for DM

Source of Variance	df	Sum of Squares	Mean Square	F-Ratio	P-Value
Between groups	3	1423.941	474.647	8.076	0.001
Error (within groups)	27	1586.925	58.775		
Total	30	3010.866			

Table 22. ANOVA table for Vc

Source of Variance	df	Sum of Squares	Mean Square	F-Ratio	P-Value
Between groups	3	948.166	316.055	2.281	0.102
Error (within groups)	27	3741.594	138.578		
Total	30	4689.76			

Table 23. ANOVA table for %SaO₂

Source of Variance	df	Sum of Squares	Mean Square	F-Ratio	P-Value
Between groups	3	190.072	63.357	85.057	<0.0001
Error (within groups)	27	20.112	0.745		
Total	30	210.184			

Table 24. CORRELATION COEFFICIENTS for %SaO₂, DLco, Vc, and DM.

%SaO₂

	Baseline	Maximal	90%	60%	30%
DLco 21% O₂	0.11	0.43	0.32	-0.01	-0.38
DLco 90% O₂	0.21	0.37	0.22	0.21	-0.37
Vc	0.26	0.23	0.11	0.36	-0.30
DM	-0.14	0.54	0.46	-0.31	-0.28

Table 25. CORRELATION COEFFICIENTS for DLco, Vc and DM.

DLco 21% O₂

	Baseline	Maximal	90%	60%	30%
DLco 90% O₂	0.95**	0.99**	0.98**	0.94**	0.93**
Vc	0.81**	0.93**	0.90**	0.77**	0.73*
DM	0.84**	0.93**	0.94**	0.91**	0.83**

*Significant correlation (p<0.05); ** (p<0.01).

Table 26. CORRELATION COEFFICIENTS for VO₂, DLco, Vc, DM, and %SaO₂.

VO₂ (ml·kg⁻¹·min⁻¹)

	Maximal	90%	60%	30%
DLco 21% O₂	-0.62	-0.21	-0.20	.021
DLco 90% O₂	-0.59	-0.12	-0.05	0.08
Vc	-0.47	-0.10	0.09	-0.03
DM	-0.67*	-0.32	-0.39	0.35
%SaO₂	-0.56	-0.33	0.13	-0.26

* Significant correlation (p<0.05).