CAN ALTERED BODY POSITION ALLEVIATE POST-EXERCISE PULMONARY DIFFUSING CAPACITY IMPAIRMENT?

by

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ABSTRACT

Pulmonary diffusing capacity for carbon monoxide (Dlco), alveolar-capillary membrane diffusing capacity (Dm), and pulmonary capillary blood volume (Vc) are all significantly reduced following exercise. It is unknown if measurement position affects this impaired gas transfer post-exercise. Prior to (baseline) and 15 minutes, 1, 2, and 4 hours following an incremental cycle to fatigue Dlco, Dm, and Vc were recorded in 10 healthy male subjects in both a supine and upright seated position. It was expected that the supine post-exercise measurement position would significantly reduce the decrement in Vc and thus Dlco, by facilitating a return of blood to the thoracic cavity.

With removal of the 15 minute data, due to the lack of achievement of a resting cardiovascular state (heart rate, systolic and diastolic blood pressure all significantly different from baseline), a significant reduction in Dlco, Dm, and Vc was observed 1, 2, and 4 hours post-exercise, as indicated in Table 1.

Table 1. Dlco, Dm, and Vc mean values for supine and seated combined corrected for alveolar volume.

	Baseline	1 hr	2 hrs	4 hrs
Dlco ($ml.min^{-1}.mmHg^{-1}.L^{-1}$)	5.51±1.03	4.72±0.94*	4.76±0.87*	4.79±0.89*
Dm ($ml.min^{-1}.mmHg^{-1}.L^{-1}$)	7.09±1.19	6.11±0.31*	6.24±1.06*	6.20±1.03*
Vc ($ml.L^{-1}$)	15.09±4.91	12.80±3.98*	12.07±3.74*	12.76±3.89*

* significantly different compared with baseline ($p<0.05$)

There was a significant difference between positions for Dlco (4.66±0.98 vs. 5.22±0.89, seated vs. supine, p=0.022) and Dm (6.28±1.36 vs. 7.00±1.32, seated vs. supine, p=0.016), but there was no position effect for Vc. Nor was there any significant interaction between the positions over time for Dlco, Dm, or Vc. The change in Dlco appears to be primarily due to a decrease in Vc. The limited decrease in Dm in the supine position was likely due to a redistribution of blood within the lung, due to gravity, enhancing the surface area available for diffusion. Although the mechanism for the reduction in Vc cannot be determined from this data, a passive relocation of blood into the periphery due to gravity can be discounted, indicating that active vasoconstriction of the pulmonary vasculature and/or peripheral vasodilatation maybe occurring post-exercise. This is the first data to indicate that the maintained diffusion impairment is independent of measurement position.

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INTRODUCTION

Since the initial research of Krogh (1914) the diffusing capacity of the lung (Dl) has been studied mainly using techniques involving carbon monoxide (Dlco). The American Thoracic Society guidelines (1995) recommend an upright seated position be utilized for Dlco measurements. However, the effect of changing body position on Dlco is not a new phenomenon, with the initial studies undertaken in the 1950s by Bates and Pearce (1956) and Ogilvie et al. (1957). These researchers first described the increase in Dlco upon changing from a sitting to a supine position. Traditional explanations for this increase in Dlco has been attributed to an increase in pulmonary capillary blood volume (Vc) in the upper pulmonary lobes (Lewis, 1958; Daly, 1964; Newman, 1962). However, the capillaries in the upper regions of the lung are not fully recruited because of the relatively low vascular pressure there. Thus, although Vc is substantially elevated, the rise in Dlco's other sub-component, the alveolar-capillary membrane diffusing capacity (Dm), is small (Chang, 1992; Prisk 1993).

Dlco is impaired after exercise of various duration and intensities (Caillaud et al, 1995; Manier et al, 1993; Sharratt et al, 1996; Stewart et al, 1997). The post-exercise restriction of Dlco persists for at least 6 hours (Sheel, 1995); and the pre-exercise Dlco is not re-established for 1-2 days (Rasmussen et al, 1988; 1992; Sheel, 1995). The post-exercise reduction reflects a decrease in both Dm and Vc. Several mechanisms have been suggested to explain the impairment: (1) a reduced central blood volume (Hanel et al, 1994, 1997); (2) acute subclinical interstitial pulmonary edema (Caillaud et al, 1995; Marsahll et al, 1971; Rasmussen et al, 1988); and/or (3) microvascular injury to the alveolar-capillary membrane (West et al, 1991).

The pulmonary blood-gas barrier measures only 0.2-0.4 μm (Gehr et al, 1978) in thickness over half its area. The reason for the extreme thinness is that movement of oxygen and carbon

dioxide through the barrier is governed by passive diffusion, and the resistance is therefore proportional to the barrier thickness. In elite animal athletes such as the racehorse, pulmonary capillary pressures rise to about 100 mmHg, resulting in stresses on the capillary walls of 5-10 x 10^4 $N.m^{-2}$. Pressures of such magnitude cause ultrastructural changes to the capillary endothelial layer, alveolar epithelial layer, or on some occasions all layers of the blood-gas barrier (West et al, 1991; Tsukimoto et al, 1991). Race horses commonly bleed into their lungs during exercise due to stress induced failure of the pulmonary capillaries.

During exercise maximal hydrostatic pressures in human pulmonary capillaries are not accurately known; they are estimated to be in the magnitude of 30-40 mmHg (Wagner et al, 1986; Groves et al, 1987; Reeves et al, 1990). Although the pressures in humans are much lower than in the racehorse, these pressures are still in the range where stress failure of the pulmonary capillaries has been demonstrated on experimental animals (West et al, 1991; Tsukimoto et al, 1991). When pressures develop in this range, the vascular endothelium may be injured allowing the movement of fluid from the vascular space to the interstitium of the lung. Stress failure of the pulmonary capillaries at these elevated pressures may cause temporary pulmonary edema. Pulmonary edema may also develop from an increased blood volume in the distended lung capillaries increasing permeability and promoting fluid shifts (Rasmussen, 1988). An associated inability of the pulmonary lymphatic system to clear the accumulated fluid may explain the depressed post-exercise Dm.

Post-exercise blood pooling in the periphery and a shunting of blood away from the thoracic cavity to clear the metabolic by-products of exercise have been suggested as mechanisms to explain the decrement in Vc following exercise (Sheel, 1995; Lama, 1995; Johnson, 1961). Thoracic electrical impedance is elevated after exercise indicating a lower thoracic fluid volume

(Hanel et al, 1994; Rasmussen et al, 1992) and supporting the reduced central blood volume theory.

If a change in body position at rest results in an increased venous return and thereby promotes an increase of blood in the pulmonary capillaries, then a post-exercise supine body position should augment the reduced Vc. Major methodological problems associated with the only two attempts to investigate this phenomenon has left the question still unresolved. Hanel et al. (1997) investigating the redistribution of blood volume from the central vascular bed to more distal regions following exercise, reported a decrease in Dlco in both seated and supine positions (6 and 12%, respectively). A corresponding change in thoracic-to-thigh electrical impedance ratio (+14%), in the seated position only, supported the authors hypothesis explaining the post-exercise decrease in Dlco. The seated and supine measurements were conducted in the same testing session, separated by 15 minutes, despite the recovery being solely in a supine position. Stewart et al. (1997) found that after one hour of recovery in a supine position Dlco and Dm were both significantly increased (14 and 16%, respectively), while Vc showed no statistically significant change from the pre-exercise seated value. Confirming previous research, one hour of seated recovery resulted in a significant decrease in Dlco (-10%), Dm (-10%), and Vc (-11%). Methodologically the supine values were not true reflections of an exercise effect alone as the baseline Dlco measurement was conducted in a seated position.

The independent changes in Dlco associated with a change in body position and recovery from exercise have been confirmed on many occasions (Chang et al, 1992; Prisk et al, 1993; Miles et al, 1983; Rasmussen et al, 1992), but the interaction of these two treatments remains unresolved despite recent investigation. The main purpose of this study was to identify the mechanisms responsible for the impaired post-exercise Dlco, Dm, and Vc, by attempting to reverse the situation. It was hypothesized that if the post-exercise decrease in Dlco and Dm was a

function of a relocation of blood into the periphery causing a decrease in Vc, then by placing the subject in a supine position the enhanced venous return post-exercise should limit the decreased central blood volume and return Vc toward baseline supine levels compared with the post-exercise upright seated levels which would remain depressed.

METHODOLOGY

Subjects

Ten healthy non-smoking males were recruited. All subjects were members of the University of British Columbia Varsity rugby team, aged between 19-25 years and had a $\dot{V}O_2$ max > 55 $ml.kg^{-1}.min^{-1}$ or 4.0 $l.min^{-1}$. Additionally, all subjects were required to have normal pulmonary function with no known history of cardiovascular or respiratory disease. Subjects who satisfied these criteria were included in the study. Prior to any testing, subjects received a verbal description of the experiment, and completed a written consent form. This study was approved by the Clinical Screening Committee for Research and Other Studies Involving Human Subjects of the University of British Columbia.

Experimental Protocol

Subjects were required to report to the laboratory on two separate occasions, separated by at least 72 hours. Anthropometric data was obtained at the first session, including age, height, and body mass. Each testing session followed a similar protocol. Subjects were required to rest for 15 minutes prior to the measurement of diffusing capacity for carbon monoxide (Dlco) in order to stabilize the pulmonary system (Billiet, 1971). Normal pulmonary function was assessed by a Collins Plus DS II Pulmonary Function Testing Unit (Warren E. Collins Inc., Braintree MA) and consisted of several flow : volume maneuvers to determine forced vital capacity (FVC), forced expiratory flow at 25-75% of FVC ($FEF_{25-75\%}$), maximal forced expiratory flow rate (FEF_{max}), forced expiratory volume in the first second (FEV_1) and peak expiratory flow rate (PEFR). Baseline values of Dlco were also obtained. Following respiratory measures, a maximal cycle ergometer test was undertaken. A total of five diffusion measurements were made, including one

pre-exercise baseline measure and four post-exercise measurements at 15 minutes, 1, 2, and 4 hours following the maximal cycle test. Blood pressure and heart rate were also recorded at each Dlco measurement. The two testing sessions differed only in the body position of the subject during the diffusion and pulmonary function measurements. Two positions were investigated, supine and seated. At all diffusion measurement periods hemoglobin concentration was measured using a direct reading hemoglobinometer (HemoCue, Helsingborg, Sweden) to correct Dlco measures (Cotes et al, 1972).

Maximal Cycle Ergometer Test

Subjects were asked to avoid exhaustive exercise for 24 hours, caffeine for 12 hours, and food and drink for 2 hours prior to testing. A self-selected 5 minute warm-up was conducted before performing the maximal exercise test. All cycling was performed, in an upright seated position, on an electronically braked cycle ergometer (Quinton Excalibur, Lode, Groningen, Netherlands). The maximal exercise test consisted of subjects cycling at a self-selected cadence against a workload increasing at 30 watts per minute until volitional fatigue. Expired gases were collected via a two-way non-rebreathing valve (Hans-Rudolph, #2700B) and analyzed with an automated metabolic system (Rayfield System). Oxygen consumption ($\dot{V}O_2$), minute ventilation ($\dot{V}e$), production of carbon dioxide ($\dot{V}CO_2$), and respiratory exchange ratio (RER) were all measured. Before each testing session, the gas analyzers were calibrated with a known gas mixture and room air. Heart rate was recorded every 15 seconds using a heart rate monitor (Polar Vantage XL, Kempele, Finland), and arterial oxygen saturation (SaO_2) was measured with a pulse ear oximeter (Ohmeda Biox 3740, BOC Health Care Inc. Edison, NJ). A topical vasodilator cream (Finalgon®, Boehringer/Ingeheim) was applied to the ear lobe to increase local perfusion, prior to placement of the ear sensor. During the test, SaO_2 was recorded and graphed at 15

second intervals. Standard indicators for achieving $\dot{V}O_2$ max were used: volitional fatigue, a plateau in $\dot{V}O_2$ with increasing work rate, heart rate ≥ 90% of age predicted maximum, and a respiratory exchange ratio ≥ 1.15. Given that three of the preceding criteria were meet $\dot{V}O_2$ max was determined by averaging the 4 highest consecutive 15 second values.

Pulmonary Diffusion Data Collection

Pulmonary diffusing capacity was determined by the single-breath method of Roughton and Forster (1957) as modified by Ogilvie et al. (1957). Single breath methods, as opposed to steady state measurements, of diffusion are thought to better reflect the alveolar membrane and pulmonary capillary characteristics of the ventilated parts of the lungs (Forster et al, 1986). Moreover, they do not require the measurement of arterial PCO_2 for their most accurate determination. The single-breath technique required that the subjects make a maximal inspiration from residual volume of a gas mixture containing 20.9% O_2, 9.7% He, 0.3% CO balanced with N_2. The breath is held for approximately 10 seconds, and then expired. The first liter of expired gas was discarded, and the next 750 ml was considered to be an alveolar sample uncontaminated by dead space gas. Concentrations of CO were measured using an infrared analyzer. For all measurements of Dlco subjects were encouraged to relax against a closed glottis and remain calm during the breath-hold in order to avoid performing a Valsalva or Muller maneuver which could lead to a decreased or increased Dlco, respectively. Each diffusion measurement was visually examined to ensure that the inspired volume was at least 90% of the FVC, the total time of inspiration was less than 2 seconds and breath-hold time between 9 and 11 seconds as determined by the methods of Ogilvie et al. (1957). Measurements were made in duplicate separated by 5 minutes to ensure elimination of the test gas from the lungs. Both tests were within 10% or 3 $ml.min^{-1}.mmHg^{-1}$ or a third test was performed (American Thoracic Society, 1995). The average

of the two closest values was recorded. The diffusion apparatus was calibrated daily for both volume and carbon monoxide.

Calculation of Diffusing Capacity

Dlco is the volume of carbon monoxide diffusing across the alveolar membrane per mmHg partial pressure change from alveolar air to mixed pulmonary capillary blood.

Equation 1. Basic Equation for Diffusing Capacity

$$Dlco = \frac{\dot{V}co}{P_ACO - Pc'CO}$$

where Dlco = diffusing capacity of CO
$\dot{V}co$ = volume (ml) of CO transferred per minute
and $P_ACO - Pc'CO$ = difference between mean alveolar and capillary CO partial pressure

In the single breath procedure, the lungs may be considered a closed bag (of volume VA) from which CO is removed at an exponential rate proportional to its concentration gradient. Under normal circumstances, the pulmonary capillary CO partial pressure ($Pc'CO$) is negligible and ignored. Dlco at breath hold time (t) may be calculated from measurements of the initial and final alveolar fraction, if the alveolar volume, is known.

Equation 2. The Krogh Equation

$$Dlco = \frac{\dot{V}_A \times 60}{713 \times t} \times Ln \frac{F_ACO_o}{F_ACO_t} \times BTPS$$

where $\dot{V}_A$ = alveolar volume
t = breath hold time
Ln = natural logarithm

$FACO_0$ = initial alveolar CO concentration
$FACO_t$ = alveolar CO concentration at the end of breath hold
BTPS = body temperature and pressure saturated

In the single breath procedure, an inert gas that will not diffuse across the alveolar membrane (usually helium (He)) is present in the inspired mixture and has two purposes, to assess the initial alveolar CO fraction from the inspired fraction, and to determine the VA via its dilution in the total lung volume. Because He does not diffuse to any great extent, the ratio of inspired He fraction to alveolar He fraction (assumed to be equivalent to the expired He fraction), will equal the ratio of inspired CO fraction to alveolar CO fraction after inspiration but before any diffusion has occurred. Thus, the initial fraction of CO ($FACO_0$) may be determined from the change in helium fraction from inspired to alveolar air multiplied by the inspired CO fraction.

Equation 3. Calculation of the initial alveolar CO fraction

$$F_ACO_o = F_ICO \times \frac{F_EHe}{F_IHe}$$

where F_ICO = inspired CO fraction
F_EHe = expired helium fraction
F_IHe = inspired helium fraction

If both sides of the equation are divided by the expired CO fraction (assumed to be equivalent to the alveolar CO concentration at the end of breath hold time ($F_ECO = FACO_t$)), the following equation is attained.

Equation 4. Calculation of the initial to final alveolar CO fraction ratio

$$\frac{F_ACO_o}{F_ACO_t} = \frac{F_ICO \times \frac{F_EHe}{F_IHe}}{F_ECO}$$

where F_ECO = expired CO fraction

As long as the change in the FCO:FHe ratio from inspired to expired gas remains proportional to changes in either CO or HE fraction, the relationship is independent of the actual quantities of inspired CO or HE. It is convenient that F_ICO is equal to F_IHe canceling these variables out of the equation.

Equation 4. (Continued)

$$\frac{F_ACO_o}{F_ACO_t} = \frac{F_EHe}{F_ECO}$$

VA may also be determined via He dilution in the total lung volume (which includes the inspired volume and the residual volume) with a correction made for the dead-space of the diffusion instrument and for anatomical dead-space (equation 5.)

Equation 5. Calculation of the alveolar volume

$$V_A = V_I - V_D \times \frac{F_IHe}{F_EHe} \times 1.05 \times BTPS$$

where V_A = alveolar volume
V_I = inspired volume
V_D = dead space (anatomical and instrument)
F_IHe = inspired He fraction
F_EHe = expired CO fraction
BTPS = body temperature and pressure saturated
1.05 = correction factor for 5% carbon dioxide in expired air removed prior to analysis

The diffusion value was adjusted for hemoglobin concentration using the formula below suggested by the American Thoracic Society in its 1995 recommendations.

Equation 6. Correction for Hemoglobin Concentration

$$\text{Dlco[Hb]adjusted} = \text{Dlcomeasured} \times \frac{9.38 + [\text{Hb}]}{1.7 \times [\text{Hb}]}$$

where Dlco [Hb]adjusted = diffusing capacity for CO corrected for [Hb] (g/dl)
Dlco measured = unadjusted diffusion measurement

Calculation of Dm and Vc

In order to calculate diffusion of the membrane (Dm) and pulmonary capillary blood volume (Vc), a second Dlco (Dlco 90% O_2) test was performed similar to the methods of Roughton and Forster (1957) and Ogilvie et al. (1957). Subjects were required to breathe for 5 minutes through a low resistance valve (Hans Rudolph, #2700B) attached to a Douglas bag filled with a gas mixture of approximately 90% O_2, and 10% N_2. The Dlco 90% O_2 test was immediately performed in the same manner as the 21% O_2. The 10 second breath hold was comprised of a gas mixture of 90% O_2, 10% He, and 0.3% CO.

The reciprocal of Dlco (1/Dlco), or resistance, is the sum of two resistance's: (1) the resistance to diffusion of CO from the alveoli through the alveolar epithelium, basement membrane and capillary endothelium and then through a plasma layer to the surface of the red blood cell (1/Dm) and (2) the resistance dependent on the rate of chemical reaction of CO with hemoglobin (θ), and the total volume of red blood cells in the pulmonary capillary bed (Vc). By adding the resistance's, an overall relationship is observed:

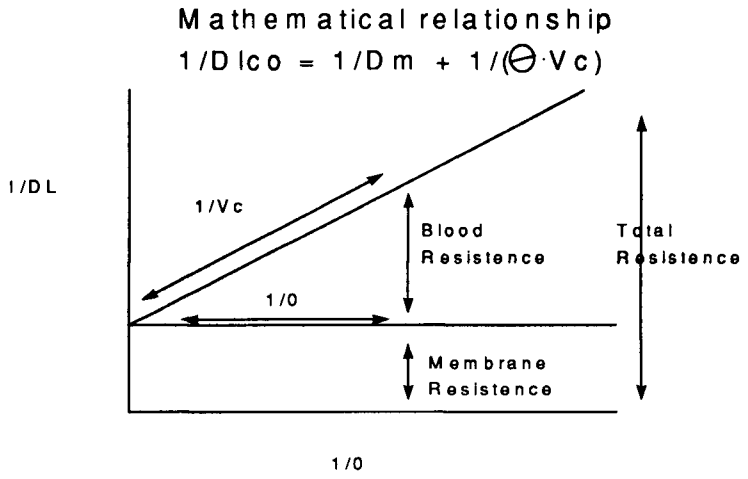


Figure 1. Roughton and Forster Mathematical Relationship

By measuring Dlco at two different inspired O_2 concentrations (Dlco 21% O_2, and Dlco 90% O_2) and plotting each value of 1/Dlco against each 1/θ, a linear regression can be formed. The slope of the line estimates 1/Vc, and the Y-intercept represents 1/Dm. Each value of 1/θ was calculated as described by Forster et al. (1986) where mean capillary oxygen ($PcapO_2$) tension can be estimated using the alveolar gas equation, assuming a respiratory exchange ratio (RER) of 0.8 and that the arterial pressure of carbon dioxide ($PaCO_2$) is equal to an alveolar PCO_2 ($PACO_2$) of 40 mmHg.

Equation 7. Alveolar Gas Equation

$$P_ACO_2 = [F_IO_2 \times (PB - 47)] - P_ACO_2\left[F_ICO_2 + \left(1 - \frac{F_IO_2}{RER}\right)\right]$$

End $PcapO_2$ is typically the same as PAO_2, while mean $PcapO_2$ is approximately 15 mmHg lower. Therefore, mean $PcapO_2$ is expressed as PAO_2 - 15. Theta, or θ, depends on the number of red blood cells present or hemoglobin concentration, [Hb]. It is therefore necessary to take [Hb] into account when calculating 1/θ. The calculated value becomes:

$$\frac{1}{\theta} = \frac{0.034 + [0.006 \times (P_AO_2 - 15)]}{[Hb]/15}$$

This technique is consistent with that performed by numerous authors (Sharrat et al, 1996; Sheel, 1995; Stewart et al, 1996; 1997) and whose reliability has been assessed by Sheel (1996) who observed a test-retest correlation for both gas measures (21% and 90% O_2) of r=0.98 and r=0.96, respectively.

Statistical Analysis

Data was examined using a 2 (position) by 5 (time) factorial analysis of variance (ANOVA) with repeated measures on both factors. Time effects were analyzed using the Dunnet Test for multiple comparisons to a control group, where post-exercise means were compared to resting values. If a significant interaction occurred, Scheffe's post-hoc procedure was applied for further comparison. *t*-tests were used to compare resting pulmonary function and other descriptive data in both positions. The level of significance was $p<0.05$ for all statistical comparisons.

RESULTS

Ten healthy male subjects completed the study (age 22.3±2.4 years, height 180.3±8.9 cm, and mass 80.4±8.6 kg). Resting respiratory function data showed no signs of abnormality (Table 1). FVC, F_{25-75}, and PEFR were all significantly ($P<0.05$) lower in the supine compared with the seated position. FEV_1 also approached significance ($P=0.058$).

Table 1. Resting pulmonary function data for both positions.

	SEATED (n=10)	SUPINE (n=10)
FVC (L)	5.59	5.16*
	(0.91)	(0.86)
FEV_1 (L)	5.18	4.46
	(0.97)	(0.64)
FEV_1/FVC (%)	87	86
	(5.64)	(4.19)
F_{25-75}% (L/sec)	5.46	4.87*
	(0.80)	(0.61)
PEFR (L/sec)	10.35	9.34*
	(1.82)	(1.85)

Values are means (± SD).
* significantly different compared with seated ($P<0.05$)

Maximal Cycle Ergometry

Results from the maximal cycle ergometer test (Table 2) showed no difference between the two testing sessions.

Table 2. Maximal oxygen consumption ($\dot{V}O_2$ max), peak power, minimal percentage of arterial oxyhemoglobin saturation (SaO_2), and maximal heart rate (HR max) obtained during maximal cycle ergometer test, session data.

	SESSION 1 (n=10)	SESSION 2 (n=10)
$\dot{V}O_2$ max (L/min)	4.26	4.22
	(0.39)	(0.41)
$\dot{V}O_2$ max (ml/min/kg)	51.82	52.39
	(3.51)	(2.12)
PEAK POWER (W)	375	376
	(29.82)	(27.69)
SaO_2 (%)	95.6	94.3
	(0.63)	(1.21)
HR max (bpm)	191	188
	(8.7)	(10.3)

Values are means (± SD).

N.B

Dlco, Dm, Vc, and VA data and ANOVA tables are presented in Appendix C. The following diffusion measurements are reported per VA, as VA was significantly higher in the seated compared with the supine position ($F=5.93$, $df=1/9$, $P=0.038$).

Pulmonary Diffusing Capacity for Carbon Monoxide per Alveolar Volume

Pulmonary diffusing capacity for carbon monoxide corrected for alveolar volume (Dlco/VA) was not significantly different between positions ($F=4.71$, $df=1/9$, $P=0.058$)[1] nor was there a significant position by time interaction ($F=1.17$, $df=4/36$, $P=0.339$). A significant time effect was found, indicating that Dlco measures were different between time periods ($F=22.89$, $df=4/36$, $P<0.001$). When compared to baseline, Dlco/VA showed no difference 15 minutes after exercise, but was significantly reduced at 1, 2, and 4 hours post-exercise ($P<0.05$) (Table 3 and Figure 1).

[1]Removal of "non-resting" data

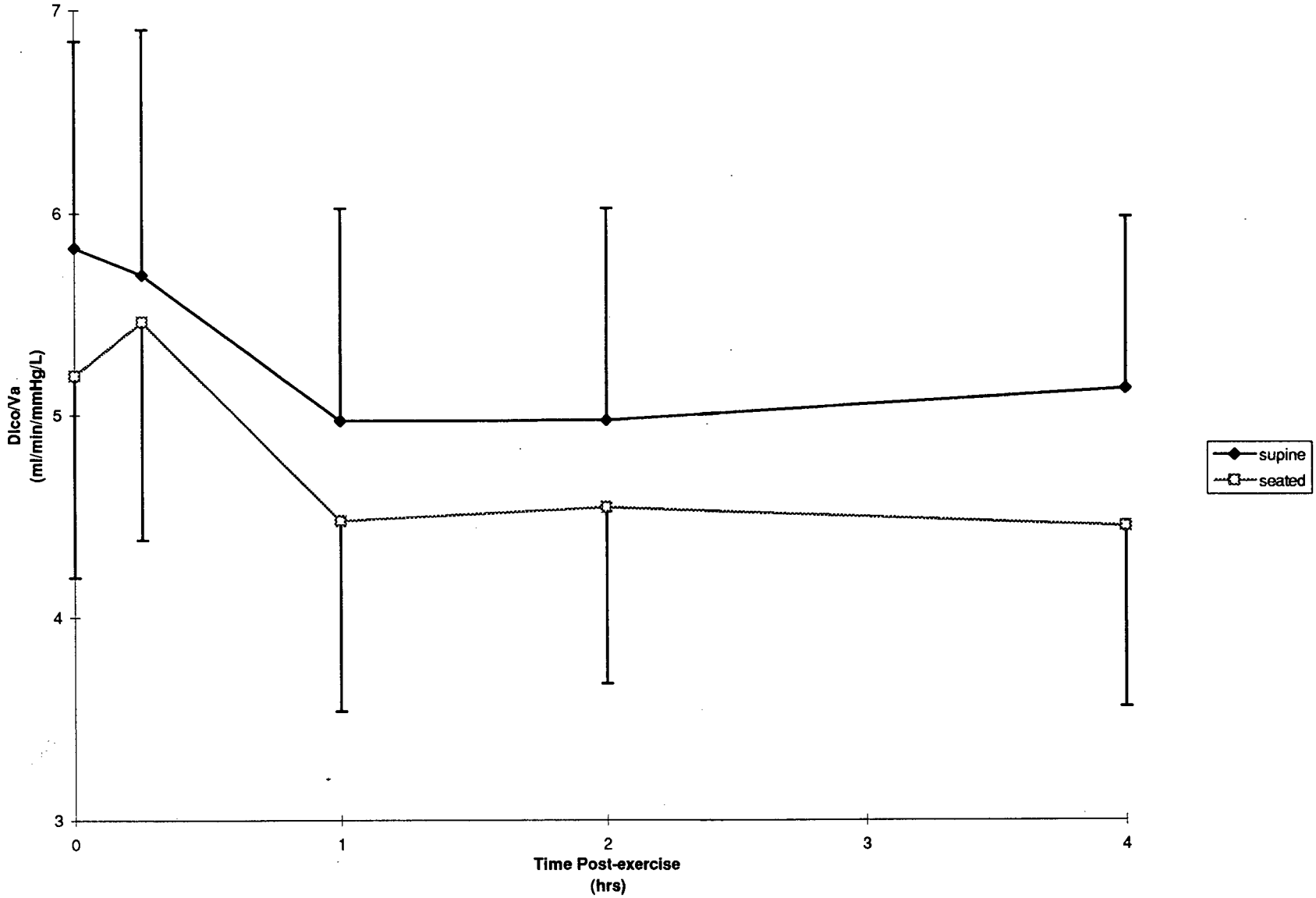
The position effect for Dlco/VA became significant (4.66 ± 0.98 vs. 5.22 ± 0.89, seated vs. supine, $p=0.022$), when the post-exercise 15 minute data was removed from the analysis. It was deemed appropriate to remove this data, due to the fact that a resting cardiovascular state had yet to be obtained (elevated heart rate 46% (Table 6) and systolic blood pressure 4% (Table 7), and a 6% decreased diastolic blood pressure (Table 8)). There was no other significant change in Dlco, Dm, or Vc, when compared with the full analysis.

Table 3. Pulmonary diffusing capacity for carbon monoxide (mL/min/mmHg), corrected for alveolar volume (L), during rest (BASE) and following maximal exercise, position data.

POSITION	BASE	15 min	1 hr	2 hrs	4 hrs
SEATED (n=10)	5.19 (1.02)	5.46 (1.21)	4.47 (1.05)	4.54 (1.05)	4.45 (0.85)
SUPINE (n=10)	5.83 (1.00)	5.69 (0.99)	4.97 (0.78)	4.97 (0.77)	5.13 (0.83)
MEAN (± SD)	5.51 (1.03)	5.58 (1.08)	4.72* (0.94)	4.76* (0.87)	4.79* (0.89)

Values are means (± SD).
* significantly different compared with baseline ($P<0.05$).

Figure 1. Pulmonary diffusing capacity corrected for alveolar volume following maximal exercise



Membrane Diffusing Capacity per Alveolar Volume

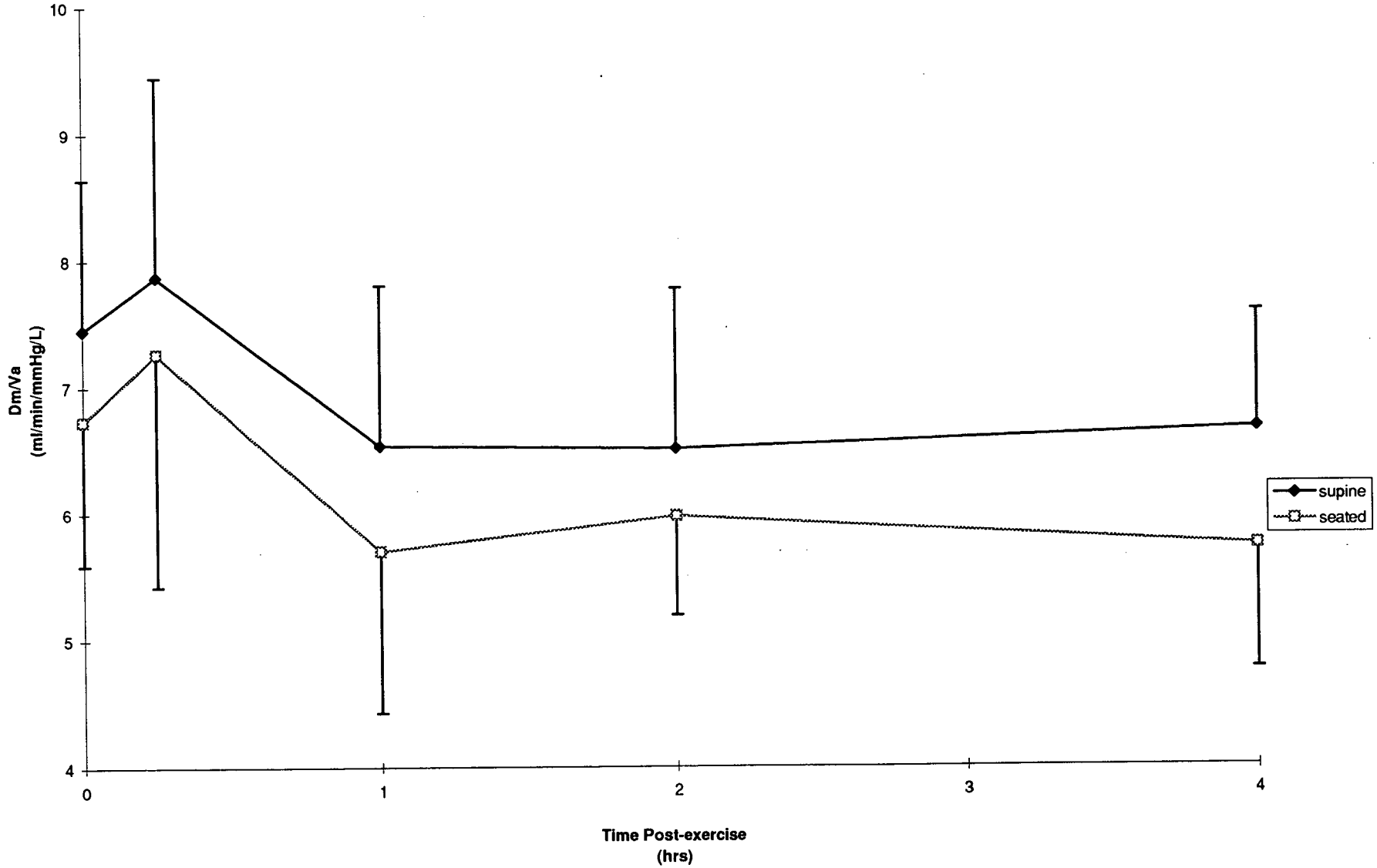
There was a significant difference between the seated and supine positions for membrane diffusing capacity corrected for alveolar volume (Dm/VA) ($F=8.75$, $df=1/9$, $P=0.016$). A significant time effect was also found ($F=17.59$, $df=4/36$, $P<0.001$), indicating that Dm measures differed over time. Further analysis showed that Dm/VA was significantly ($P<0.05$) lower at 1, 2, and 4 hours post-exercise compared with baseline, but once again no difference was noted 15 minutes after the completion of exercise. Overall mean changes are summarized in Table 4 and plotted in Figure 2. There was no significant interaction between the two positions over time ($F=0.34$, $df=4/36$, 0.848).

Table 4. Membrane diffusing capacity (mL/min/mmHg), corrected for alveolar volume (L), during rest (BASE) and following maximal exercise, position data.

POSITION	BASE	15 min	1 hr	2 hrs	4 hrs
SEATED (n=10)	6.73 (1.19)	7.26 (1.57)	5.70 (1.27)	5.97 (1.27)	5.73 (0.92)
SUPINE (n=10)	7.45 (1.14)	7.87 (1.84)	6.53 (1.27)	6.50 (0.78)	6.66 (0.97)
MEAN (± SD)	7.09 (1.19)	7.56 (1.69)	6.11* (1.31)	6.24* (1.06)	6.20* (1.03)

Values are means (± SD).
* significantly different compared with baseline ($P<0.05$).

Figure 2. Alveolar-capillary membrane diffusing capacity corrected for alveolar volume following maximal exercise



Pulmonary Capillary Blood Volume per Alveolar Volume

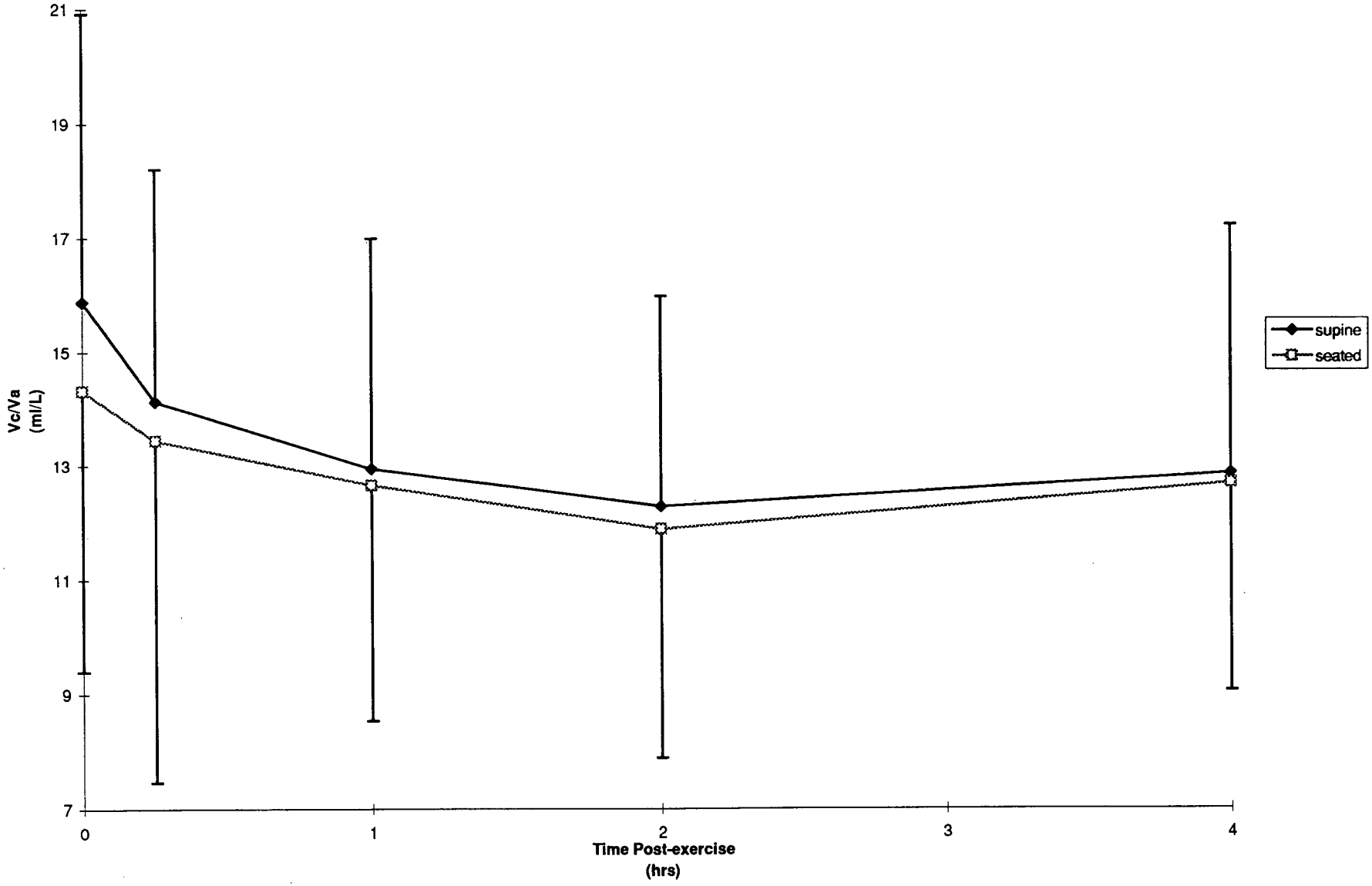
Pulmonary capillary blood volume, corrected for alveolar volume, was not significantly different between positions (F=0.26, df=1/9, P=0.623) nor was there a significant interaction between the positions over the time periods (F=0.16, df=4/36, P=0.955). There was a significant time effect (F=3.20, df=4/36, P=0.024), and post-hoc tests revealed a significant difference only between the baseline mean and 1, 2 and 4 hour post-exercise means (P<0.05) (Table 5 and Figure 3).

Table 5. Pulmonary capillary blood volume (mL), corrected for alveolar volume (L), during rest (BASE) and following maximal exercise, position data.

POSITION	BASE	15 min	1 hr	2 hrs	4 hrs
SEATED (n=10)	14.31 (5.04)	13.44 (4.08)	12.65 (4.04)	11.87 (3.69)	12.67 (4.34)
SUPINE (n=10)	15.88 (4.92)	14.12 (5.98)	12.94 (4.12)	12.27 (3.99)	12.85 (3.63)
MEAN (± SD)	15.09 (4.91)	13.78 (4.99)	12.80* (3.98)	12.07* (3.74)	12.76* (3.89)

Values are means (± SD).
* significantly different compared with baseline (P<0.05).

Figure 3. Pulmonary capillary blood volume corrected for alveolar volume following maximal exercise



Heart Rate

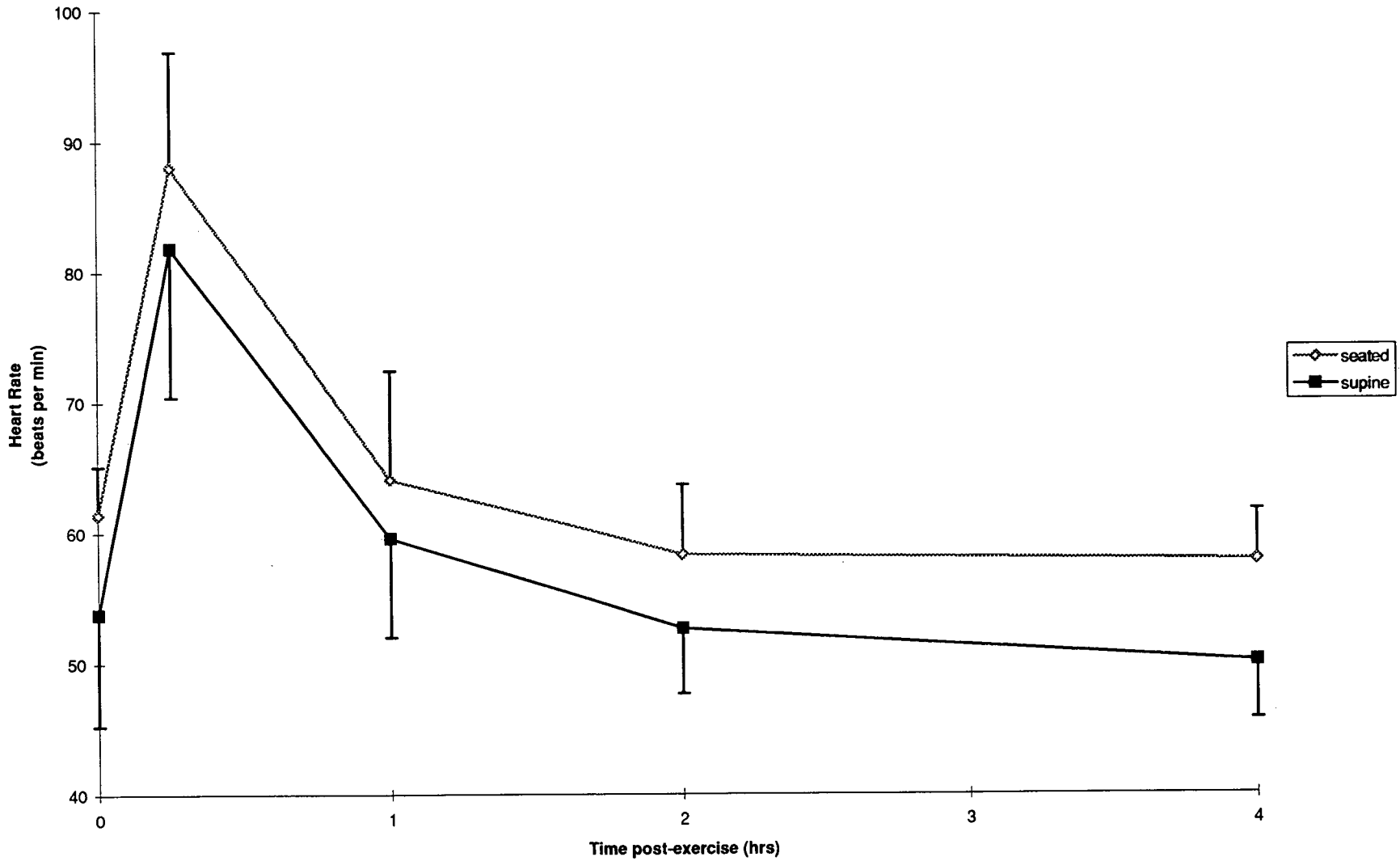
Heart rate was found to differ between the two positions ($F=17.53$, $df=1/9$, $P=0.002$) as well as over the time periods ($F=103.6$, $df=4/36$, $P<0.001$). Post-hoc analysis revealed that at 15 minutes post-exercise heart rate was significantly ($P<0.05$) elevated compared with the baseline mean value (Table 6 and Figure 4). There was no significant time x position interaction ($F=0.45$, $df=4/36$, $P=0.772$).

Table 6. Heart rate (bpm) during rest (BASE) and following maximal cycle ergometry, position data.

POSITION	BASE	15 min	1 hr	2 hrs	4 hrs
SEATED (n=10)	61.40 (3.69)	88.03 (8.84)	64.05 (8.35)	58.26 (5.40)	57.85 (3.80)
SUPINE (n=10)	53.72 (8.52)	81.81 (11.44)	59.55 (7.55)	52.61 (4.97)	50.08 (4.39)
MEAN (± SD)	57.56 (7.51)	84.92* (10.45)	61.80 (8.08)	55.44 (5.82)	53.97 (5.64)

Values are means (± SD).
* significantly different compared with baseline ($P<0.05$).

Figure 4. Heart Rate following maximal exercise



Systolic Blood Pressure

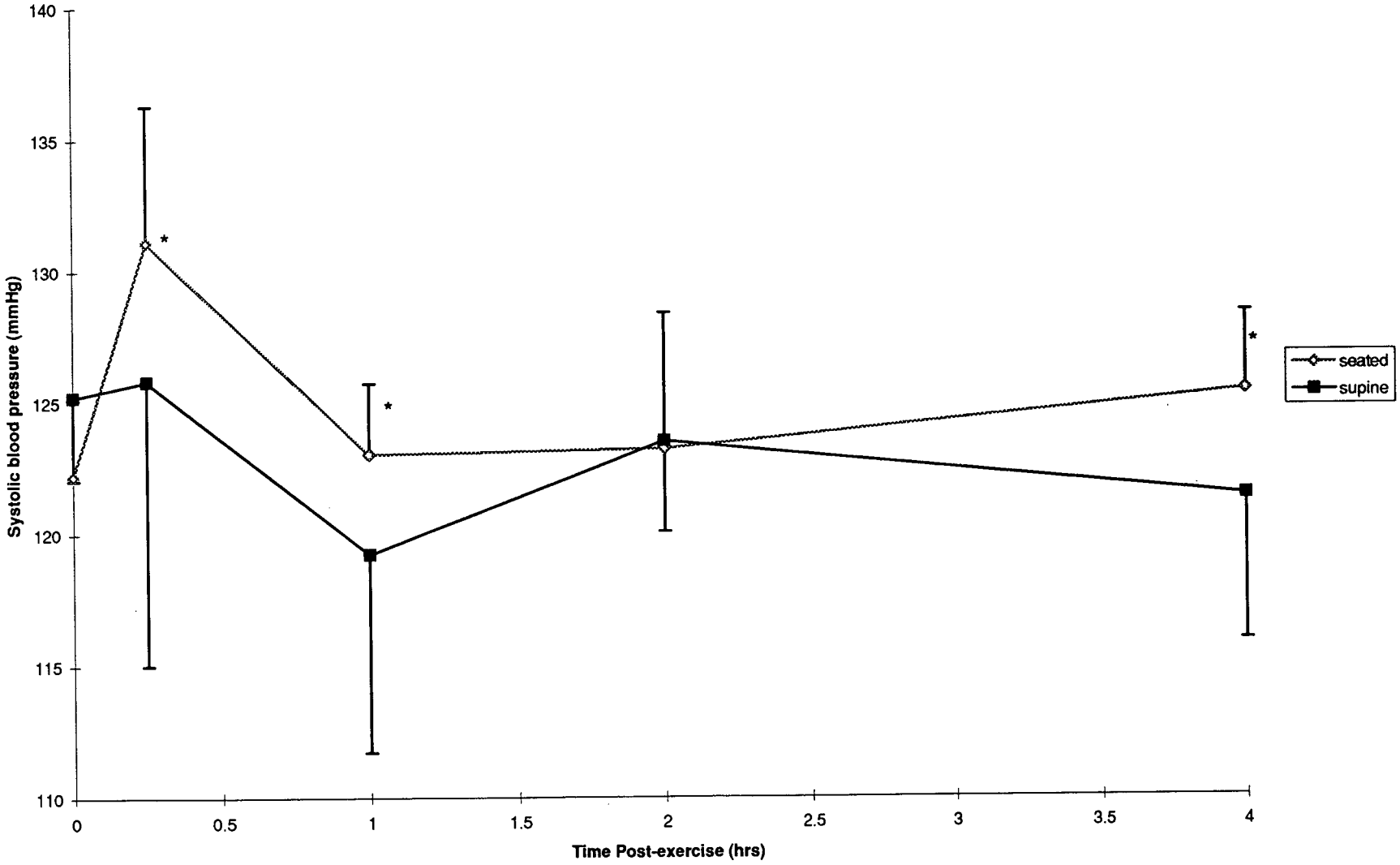
There were significant time, and position x time interaction effects (F=6.50, df=4/36, P<0.001; F=2.96, df=4/36, P=0.033, respectively) observed for the systolic blood pressure data presented in Table 7 and Figure 5. The time effect was only significant (P<0.05), when compared with the baseline mean, at the 15 minute post-exercise value. Post-hoc analysis for the interaction effect showed that the seated value was significantly higher than the supine at 15 min, 1, and 4 hrs following exercise. There was no significant difference between the overall position means (F=1.68, df=1/9, P=0.227).

Table 7. Systolic blood pressure (mmHg) at rest (BASE) and following maximal exercise, position data.

POSITION	BASE	15 min	1 hr	2 hrs	4 hrs
SEATED (n=10)	122.2 (2.90)	131.1** (5.17)	123.0** (2.71)	123.2 (5.18)	125.4** (2.99)
SUPINE (n=10)	125.2 (3.16)	125.8 (10.81)	119.2 (7.50)	123.5 (3.44)	121.4 (5.50)
MEAN (± SD)	123.7 (3.33)	128.5* (8.68)	121.1 (5.82)	123.35 (4.28)	123.4 (4.77)

Values are means (± SD).
* significantly different compared with baseline (P<0.05).
** significantly different compared with supine (P<0.05).

Figure 5. Systolic Blood Pressure following maximal exercise



* significantly different compared with supine (P<0.05)

Diastolic Blood Pressure

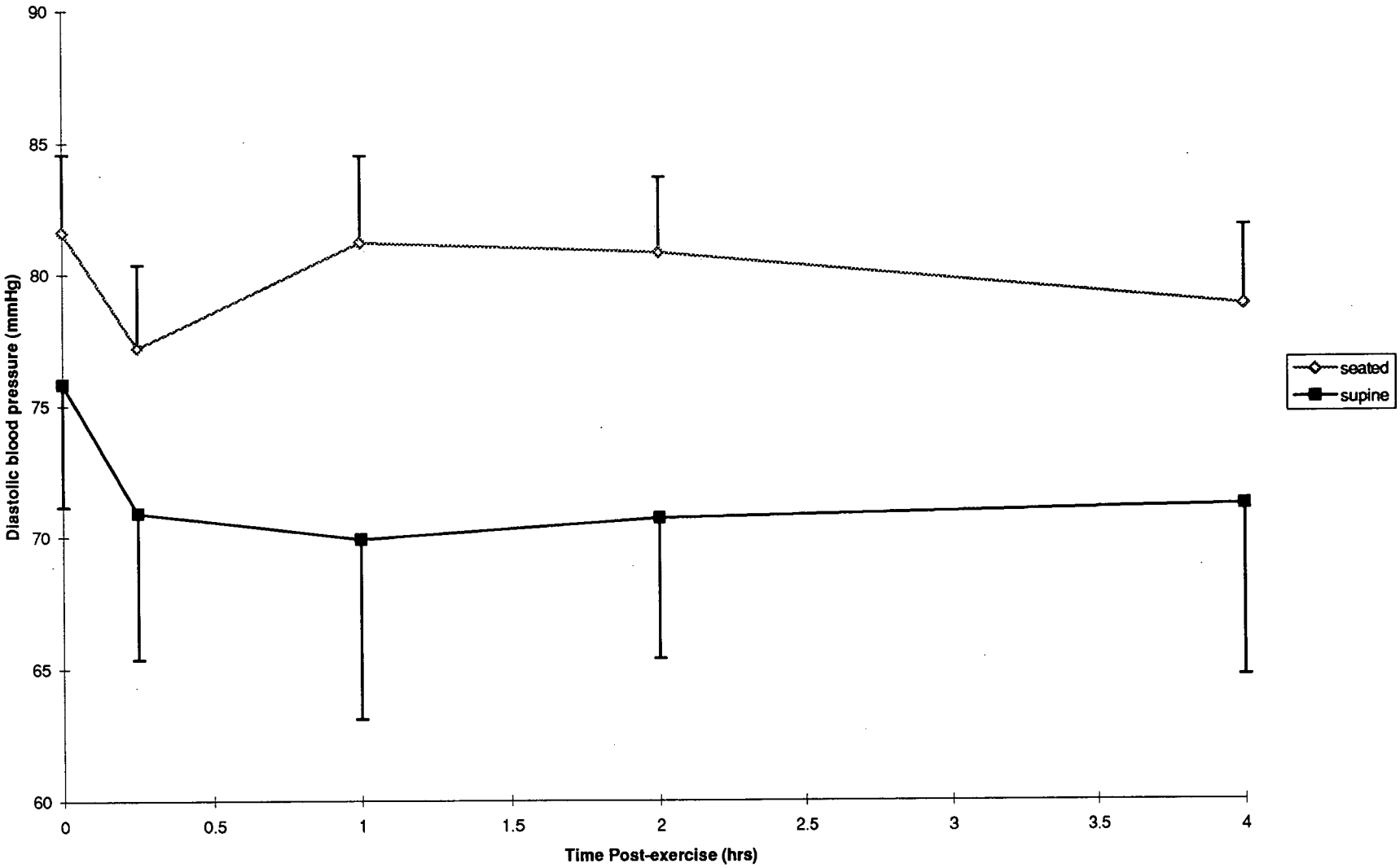
Significant time and position effects (F=4.72, df=4/36, P=0.004; F=27.83, df=1/9, P=0.001, respectively) were observed for the diastolic blood pressure values shown in Table 8 and Figure 6. Post-hoc tests showed significant (P<0.05) time effects at all post-exercise periods, 15 minutes, 1, 2, and 4 hrs, when compared with the baseline mean. There was no significant time x position interaction (F=2.59, df=4/36, P=0.053).

Table 8. Diastolic blood pressure (mmHg) at rest (BASE) ad following maximal cycle ergometry, position data.

POSITION	BASE	15 min	1 hr	2 hrs	4 hrs
SEATED (n=10)	81.6 (2.95)	77.2 (3.16)	81.2 (3.29)	80.8 (2.86)	78.8 (3.01)
SUPINE (n=10)	75.8 (4.66)	70.9 (5.55)	69.9 (6.82)	70.7 (5.33)	71.2 (6.48)
MEAN (± SD)	78.7 (4.82)	74.05* (5.45)	75.55* (7.80)	75.75* (6.65)	75.0* (6.27)

Values are means (± SD).
* significantly different compared with baseline (P<0.05).

Figure 6. Diastolic blood pressure following maximal exercise



DISCUSSION

This study confirmed that pulmonary diffusing capacity is decreased during recovery from maximal exercise and that this is the case when determined in both a supine and an upright seated position.

Maximal Cycle Ergometer Tests

Descriptive data for the two incremental cycles to volitional fatigue (Table 2) showed that an equal stress was applied to the subjects at each testing session. Peak power output, maximal oxygen consumption, and heart rate were not significantly different between the two sessions. No subjects in this study were classified as having exercise induced hypoxemia as classified by an arterial oxygen saturation of less than 91% (Powers et al, 1983).

Pulmonary Function Tests

Confirming previous reports, lung volumes were significantly lower in the supine compared with upright seated position (Table 1). Briscoe (1965) in a review of the effect of posture on lung volume subdivisions suggested the change in vital (VC), functional (FRC), and total lung capacities (TLC) were a function of a rise in the position of the diaphragm when supine reducing lung volumes more than the increase in chest girth augmented them. The other mechanism Briscoe (1965) postulated for the induced changes was the increased volume of blood in the chest. Sjostrand (1963) measured both the FRC and the volume of the trunk in a corset which functioned as a plethysmograph. He also measured chest circumference with a pneumogram. After tilting six subjects from a supine to an erect position, he observed the usual lung volume changes, notably mean increases of 335 (VC), 470 (TLC), and 725 ml (FRC), in the

erect posture. However, the resting trunk volume measured by the corset plethysmograph only increased by 285 ml. Therefore, a large part of the increase in FRC (725-285=440ml), was due to a decrease in the volume of nongaseous material in the chest, presumably blood. Likewise the increase in TLC in the erect posture was almost entirely accounted for by the decreased volume of blood in the chest since the external volume of the trunk measured in the position of maximum inspiration was only 30 ml more than when supine. It is now accepted that the reduced lung volumes in the supine position are the result of an increase in blood volume in the thoracic cavity.

Pulmonary Capillary Blood Volume

Maximal exercise resulted in a reduced Vc following exercise in both a supine and upright seated position (Table 5). Position had no effect on the magnitude of the decrement, which was still maintained 4 hours following exercise. The reduced post-exercise Vc has been reported following exercise of varying intensities, durations and modalities (Caillaud et al, 1995; Hanel et al, 1994; Manier et al, 1993; Sharratt et al, 1996; Stewart et al, 1997). It has also been documented to remain depressed for a period of 24 hours (Rasmussen et al, 1988; Sheel, 1995).

Recent attention has been given to the role of a reduced central blood volume being the primary mechanism behind the impaired Dlco post-exercise (Hanel et al, 1994; 1997). The decreased Vc found in the present study supports this theory (Table 5). Thoracic fluid volume, measured by electrical impedance, is decreased after exercise (Hanel et al, 1994; 1997; Rasmussen et al, 1992) and has been shown to be still decreased at 2-3 hours post-exercise. A parallel relationship between the post-exercise decrease in Vc and an increase in thoracic electrical impedance, indicates a reduction in central fluid volume, specifically blood. However the mechanism behind this reduction in central blood volume remains unknown.

It was hypothesized that if the post-exercise decrease in Dlco and Dm was a function of a relocation of blood into the periphery causing a decrease in Vc, then by placing the subject in a supine position the enhanced venous return post-exercise should limit the decreased central blood volume and return Vc toward baseline supine levels compared with the post-exercise upright seated levels which would remain depressed.

Inactivity for a prolonged period in the upright seated position removes the effect of the muscle pump assisting venous return, suggesting peripheral pooling of blood may be the cause of the decreased Vc. However, the lack of a position effect for Vc (Figure 3), clearly indicates that a gravity induced relocation of blood into the periphery is not the cause of the reduced central blood volume and therefore the depressed Vc.

Other possible hypotheses include a compensatory shunting, consequent to heavy exercise, as blood flow is directed away from the thorax to clear metabolic waste products from exercised muscles (Lama et al, 1996). This seems unlikely as the development of a depressed Vc after only 10 minutes of cycling at 25% $\dot{V}O_2$ max (Sharrat et al, 1996) and the increasing magnitude of the impairment up to six hours after exercise (Sheel, 1995) do not reflect the time course of metabolic waste development and clearance, respectively.

Increased thoracic electrical impedance, decreased atrial natriuretic peptide (Hanel et al, 1997), and decreased Vc all indicate a reduced central blood volume post-exercise. The mechanism responsible for this cannot be determined from this data, although previous suggestions of passive redistribution of blood due to gravity can be discounted, indicating that active vasoconstriction of the pulmonary vasculature and/or peripheral vasodilatation may be occurring post-exercise.

Alveolar-Capillary Membrane Diffusing Capacity

Following exercise, the expected decrease in Dm was observed (Table 2). This is reflected in an increase in the thickness of the alveolar-capillary membrane decreasing the rate of gas transfer between the alveolus and the red blood cell, and/or a decrease in the available surface area for diffusion.

The post-exercise decrease has been suggested to be an indicator of the development of acute pulmonary edema. Direct attempts to quantify the lung density and extravascular water content following exercise have met with varying success. The initial studies undertaken by Marshall et al. (1971) failed to detect any change in lung wet weight/dry weight ratio in dogs following vigorous exercise. Vaughan et al. (1976) made measurements of lung water by indicator dilution after exercise in man and concluded there was no detectable increase in extravascular lung water. Recently, McKenzie et al. (1996) was also unable to find any changes in lung density utilizing CT scans and magnetic resonance imaging. Following a triathlon, Caillaud et al. (1995) although unable to find any visual evidence of acute alveolar or interstitial edema, was able to detect a significant increase in mean lung density using CT scanning. It therefore appears that the duration of the exercise has a linear relationship with the amount of fluid accumulated. Extravascular lung water accumulates first in perivascular and peribronchial spaces, and thus even a small increase in lung water below the range of sensitivity of modern measurement techniques may cause the physiological changes found in the lung after exercise, as indirectly indicated by a decreased Dm.

It is also a possibility that the less depressed Dm in the supine position (Figure 2) is the result of an increased pulmonary lymph flow removing any accumulated interstitial fluid. Cardiac output has been found to be linearly related to pulmonary lymph flow (Coates et al, 1984) The significantly decreased heart rate, in the supine compared with the upright seated position (Figure

4), indirectly indicates an elevated cardiac output in the supine position. Coates et al. (1984) also speculated that the same parallel relationship would exist between pulmonary lymph flow and surface area, and concluded that the increase in the perfused microvascular surface area with exercise was the primary determinant for the increase in pulmonary lymph flow. If such a relationship exists post-exercise, then the increased cardiac output and perfused microvascular surface area in the supine position would result in an increased rate of removal of any accumulated interstitial fluid.

Dm has been found to be significantly decreased one hour after cycling at only 25 % $\dot{V}O_2$ max for 10 minutes (Sharratt et al, 1996). At this low exercise intensity it is doubtful that pulmonary capillary pressures would be very high, making physiologically significant injury unlikely, therefore another mechanism must be responsible for the impaired gas transfer other than pulmonary edema. Dm is also affected by the surface area available for diffusion, thus a decrease in Vc reducing the amount of blood in and the number of open pulmonary capillaries could explain the impaired Dm post-exercise. But Dm was significantly higher in the supine compared with upright seated position (Figure 2), despite Vc being the same in both positions (Figure 3).

The elevated Dm in the supine position compared with the upright seated position, was likely due to a gravity induced redistribution of blood from the distended capillaries in the lower zones of the lung in the upright seated position to the upper zones thereby increasing capillary recruitment and available surface area in the supine position. Bryan (1964) was the first to document a mismatch in the degree of ventilation and perfusion in different zones of the lung. He found a 1.7 ratio in the upper zone compared with a 0.9 and 0.68 ratio in the middle and lower zones, respectively. When placed in a supine position a more uniform ratio of 0.7, 0.71, and 0.74 was found in the upper through lower zones. These results have been confirmed using different techniques and on numerous occasions (Brudin et al, 1994; Glaister et al, 1967; West, 1960). This

increased uniformity in ventilation and perfusion in the supine position would increase Dm, via an increase in the surface area available for gas transfer.

Pulmonary Diffusing Capacity

This study confirmed that pulmonary diffusing capacity was impaired during recovery from maximal exercise and that this reduction persisted for at least four hours (Hanel et al, 1994; Sheel, 1995). It also supports the recent finding of Hanel et al. (1997) that the post-exercise impairment occurs in both a supine and upright seated position. At the same time as the decrease in Dlco was measured, the blood concentration of carbon monoxide was observed to increase. This however did not influence the magnitude of the decrement in Dlco (Appendix B). The changes in Dlco observed in this study were therefore not the result of carbon monoxide back pressure. Nor were they affected by a maintained elevation in cardiac output, as heart rate had returned to baseline levels when Dlco was observed to decline (Table 4).

The impaired Dlco post-exercise has been shown to have no effect on continued performance, as $\dot{V}O_2$ max, SaO_2, $PaCO_2$, pH, and notably PaO_2 were similar between repeated bouts of exercise (Hanel et al, 1994; Lama et al, 1996). The reproducibility of the exercise $\dot{V}O_2$ max and maintained PaO_2 suggest physiologically significant injury to the alveolar capillary membrane is not the mechanism responsible for the decreased Dlco and Dm, following short duration maximal exercise.

A reduction in central blood volume as indicated by the decreased Vc is the primary mechanism responsible for the impaired Dlco. The pulmonary vasculature acts as a reservoir for blood during rest (Sjostrand, 1963; Stam et al, 1991). Following exercise this reservoir may be depleted in order to return relative homeostasis to other regions of the body. The decreased Vc at low intensities (Sharrat et al, 1996) and following short duration exercise (Sheel, 1995) indicates

that this mechanism is not graded but rather an all or nothing response. The maintained depression in Vc following many hours of recovery indicates that the replenishment of this reservoir is not a priority of the body.

Summary

The results of this study confirm that pulmonary diffusing capacity is reduced following an incremental cycle to volitional fatigue. It is also the first data to indicate that the maintained diffusion impairment is independent of measurement position. The change in Dlco appears to be primarily due to a decrease in Vc. The augmented decrease in Dm in the supine position was due to a redistribution of blood within the lung, due to gravity, enhancing the surface area available for diffusion. The decrease in Vc has previously been attributed to a reduced central blood volume. Although the mechanism for this reduction cannot be determined from this data, previous suggestions of a passive relocation of blood into the periphery due to gravity can be discounted, indicating that active vasoconstriction of the pulmonary vasculature and/or peripheral vasodilatation may be occurring post-exercise.

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APPENDIX A

REVIEW OF LITERATURE

PULMONARY DIFFUSING CAPACITY: RECOVERY FROM EXERCISE AND MEASUREMENT POSITION

INTRODUCTION

The process of diffusion is governed by Fick's law, where the rate of transfer of a gas through tissue is proportional to the tissue surface area and the difference in gas partial pressure between the two sides, and inversely proportional to the tissue thickness. Measurement of the diffusing capacity of the lung with carbon monoxide is based on the initial work of Krogh (1914), which was subsequently modified by Roughten and Forster (1957) and Ogilvie et al. (1957). Carbon monoxide is used as its affinity for Hb is ≈200X that of oxygen. The diffusion capacity of the lung from alveoli to pulmonary capillary blood is partitioned into two separate components. The membrane diffusing capacity is the transfer of gas from the alveoli to the red blood cell, including the plasma. Once added to the blood, the combination of gas (NO, O_2 or CO) with hemoglobin is represented by θ, and the amount of blood in the vascular bed (Vc). The total resistance of the lung is thus represented by the mathematical equation developed by Roughten and Forster:

$$\frac{1}{Dlco} = \frac{1}{Dm} + \frac{1}{\theta \cdot Vc}$$

The ability for oxygen to diffuse through the lung can therefore be affected by anything that may result in a change in either of Dlco's two components.

Factors which increase Vc include the use of a G suit (Krumholz, King and Ross, 1963), water immersion (Guyatt et al, 1965), and exercise (Ayers, 1975). Conversely, head up tilting

(Daly, Krumholz and Ross, 1964), lower body negative pressure (Zechman et al, 1967) and an increase in environmental temperature (Frayser et al, 1966) will lead to a decrease in Vc.

Dm represents the diffusing capabilities of the alveolar-capillary membrane. Included within this broad term are the surface area and physical properties of the alveolar surface film, the alveolar epithelium, the connective tissue space, the capillary endothelium and the blood plasma. Dm may also be influenced by the biochemical properties and the enzyme content of the membrane. Factors that increase Dm primarily and not as a result of an increase in Vc causing capillary recruitment and thereby enhancing the available surface area for gas exchange, include: an increase in ventilation homogeneity with respect to diffusion surface so as to reduce the dispersion of Dm to blood flow and ventilation to diffusion ratios (Pistelli et al, 1991). Dm is decreased in the presence of an increase in thickness of the alveolar-capillary membrane in such pathological conditions as pulmonary edema, diabetes, scleroderma, sarcoidosis, asbestosis, beryllosis, and interstitial fibrosis (Forster, 1965).

The following literature review will concentrate on the effect of exercise and the recovery from it and also the effect of measurement position on Dlco.

EXERCISE AND RECOVERY

During strenuous exercise, Dlco increases 2-3 fold due to recruitment of pulmonary capillaries and an increase in cardiac output (Ayers, 1975). Strikingly, several studies have shown that Dlco is significantly reduced following strenuous short-term exercise (Manier, 1993; Rasmussen et al, 1991; Sheel, 1995; Stewart et al, 1996; 1997) and long-term exhaustive exercise (Caillud et al, 1995; Manier et al, 1991; Miles, 1983). Two major hypotheses have been suggested to explain the decrease in post-exercise Dlco including the development of subclinical interstitial

pulmonary edema or injury to the alveolar-capillary membrane (Caillaud et al, 1995) and/or a reduction in central blood volume (Hanel et al, 1997).

Acute Pulmonary Edema

The mechanism of the edema formation is unclear, but it is likely related to an increase in capillary hydrostatic pressure, capillary permeability, capillary surface area and/or a lymphatic insufficiency (West, 1977). Mean pulmonary arterial pressure and capillary wedge pressures can reach values greater than ~ 40 and 27 torr, respectively (Wagner, 1986; Reeves, 1988). Stress failure of the pulmonary capillaries at these elevated pressures may cause leakage of fluid and temporary pulmonary edema. When pressures develop in this range, the vascular endothelium may be injured allowing the movement of fluid from the vascular space to the interstitium of the lung. Another possibility is that the increased blood volume in the distended lung capillaries could result in increased permeability and thus promote fluid shifts (Rasmussen et al, 1988).

Accumulation of interstitial fluid is usually removed by the lymph flow, but the lymphatic system may become overloaded. Pulmonary lymph flow has been shown to parallel the changes in cardiac output (Coates et al, 1984; Marshall et al, 1971). In exercising sheep, Coates et al. (1984) measured a three fold increase in lung lymph flow, which returned to baseline with the return of cardiac output to baseline. Lung lymph flow has also been documented to have returned to baseline levels after the end of exercise, despite the fact that the subjects were still hyperventilating (Coates et al, 1983; Pang et al, 1982). Therefore discounting respiratory rate as the driving force for pulmonary lymph flow. While unable to measure the surface area of the exchanging vessels within the lung, Coates speculated that the same parallel relationship would exist between lymph flow and surface area as measured between cardiac output and lymph flow. Coates thus concluded that the increase in the perfused microvascular surface area with exercise was the primary determinant for the increase in lymph flow.

To date no direct evidence of increased lung water following exercise has been discovered. The initial studies undertaken by Marshall et al. (1971) failed to detect any change in lung wet weight/dry weight ratio in dogs following vigorous exercise. Vaughan et al. (1976) made measurements of lung water by indicator dilution after exercise in man and concluded there was no detectable increase in extravascular lung water. Recently McKenzie et al. (1996) was also unable to find any changes in lung density utilizing CT scans and magnetic resonance imaging. Following a triathlon, Caillaud et al. (1995) although unable to find any visual evidence of acute alveolar or interstitial edema was able however to detect a significant increase in mean lung density using CT scanning. It therefore appears that the duration of the exercise has a linear relationship with the amount of fluid accumulated. Extravascular lung water accumulates first in perivascular and peribronchial spaces, and thus even a small increase in lung water below the range of sensitivity of modern measurement techniques may cause the physiological changes found in the lung after exercise, as indirectly indicated by a decreased Dm.

Reduced Central Blood Volume

Recent attention has been given to the role of a reduced central blood volume being the primary mechanism behind the impaired Dlco post-exercise (Hanel et al, 1994; 1997). Thoracic electrical impedance, an index of fluid volume, is elevated after exercise (Hanel et al, 1994; 1997; Rasmussen et al, 1992) and has been shown to be still elevated 2-3 hours post-exercise. A parallel relationship between the post-exercise decrease in Vc and an increase in thoracic electrical impedance, indicates a reduction in central fluid volume, specifically blood. The mechanism behind this reduction in central blood volume remains unknown.

Inactivity in the prolonged upright seated position removes the effect of the muscle pump assisting venous return, suggesting peripheral pooling of blood may be the cause of the decreased Vc (Johnson et al, 1961). Other possible hypotheses include a compensatory shunting consequent

to heavy exercise, as blood flow is shunted away from the thorax to clear metabolic waste products from exercised muscles (Lama et al, 1996).

Post-exercise Recovery

If pulmonary edema and/or a reduction in central blood volume develops as a result of exercise causing a decrease in Dlco, then there should be a necessary time period before homeostasis is observed. Maron et al. (1979) was the first to investigate post-exercise pulmonary diffusion and discovered that following a marathon run there was no change in Dlco. However, a significant correlation existed between the change in Dlco and the heart rate at the post-exercise measurement. This is indicative of an elevated cardiac output, which can be responsible for overestimating Dlco. Conversely, others have shown statistically significant decreases in Dlco post-exercise. Miles et al. (1983) was the first to partition Dlco following exercise and found that both Dlco and Dm decreased following a marathon. This occurred despite the return of Vc and heart rate to normal 1-2 hours after the completion of exercise. These results are supported by Manier et al. (1991) who analyzed the diffusion capacity of the lung for both carbon monoxide and nitric oxide following a marathon. Both post-race measures were depressed when compared to pre-race values. 24 hours post-exercise mean Dm was still decreased 29% while Vc had returned to pre-race values. Sheel (1995) also observed a continuing decrement in Dlco 2, 4, 6, and 24 hours after short duration exercise. This was reflected in a parallel decrease in Vc, while Dm was not significantly reduced until the 6^{th} hour of recovery.

The duration and intensity of the exercise protocol utilized and the timing of the post-exercise measurements have a dramatic effect on Dlco. Sharrat et al. (1997) found that with increasing intensity of exercise there was a corresponding decrement in Dm. There appeared to be a threshold effect in the change in Dlco since at intensities of 25 and 50% peak power the change

in Dlco was of the same magnitude, while 75% elicited a decrease approximately twice that of the lower intensities. Intensity had no effect on post-exercise Vc.

In a recent study investigating the effect of a reduced Dlco on a second bout of exercise, Hanel et al. (1994) placed the subjects in a supine position for periods between 2 and 6 hours, but surprisingly all Dlco measurements were conducted in a seated position. Two hours following exercise Dlco, Dm, and Vc were all significantly reduced compared with baseline. Following a further 2 hours supine recovery Dlco levels remained depressed, due entirely to Vc which continued to fall, while Dm returned to baseline values. Although not statistically significant, a trend towards an increase in thoracic electrical impedance, lead the authors to suggest that a reduction in central fluid volume was responsible for the decline in Dlco and Vc post-exercise. By placing the subject in a supine position following exercise Hanel was increasing the area of lung being perfused. This undoubtedly enabled an increase in lymph flow to remove any edema which had accumulated post-ex, thereby returning Dm to baseline levels. The continued decrement in Vc post exercise reported by Hanel, does not support the hypothesis of an increase in the area of the lung being perfused. However the change in body position undertaken by Hanel's subjects, immediately prior to measurement, would have resulted in a large relocation of blood volume from the thoracic cavity due to gravity. Hirasuna and Gorin (1981) described a 50% change in Vc 5 minutes after moving from a seated to supine position. Hanel made no comment on how soon before the measurements were conducted that her subjects assumed a seated position, but a similar dramatic change in pulmonary capillary blood volume may be expected when moving in the opposite direction. If the decrement in Vc caused the area of the lung being perfused to drop, then for Dm to remain at baseline levels the membrane component must also be reduced compared with baseline levels. While physiologically this sounds like a marvelous idea to reduce the distance the oxygen molecule has to travel to combine with Hb, it is at the same time

impossible, therefore the number of capillaries being perfused did not decrease but the volume of blood within the open capillaries did.

SUPINE PHYSIOLOGY

In recumbent man more than 50% of the total blood volume is contained in the systemic veins, about 30% in the intrathoracic vessel compartments, and less than 15-20% in the systemic arteries. Volume shifts therefore are almost entirely confined to the low-pressure system. Since on assumption of the upright position intravascular pressures decrease above the Hydostatic Indifference Point (HIP) and rise in the dependent parts of the body, large displacements of blood volume are to be expected. The most extensive pressure increase must take place in the leg veins. From the length of the legs and the measured intravenous pressure at the ankle (120 to 130 cm H_2O), the mean distending pressure may be estimated; it is approximately 80 cm H_2O. The amount of blood pooling when the pressure rises from 15 cm H_20 during recumbency to this level may be derived from the pressure volume diagram for both legs up to the groin; it is approximately 500 ml.

Using a combination of spirographic and plethysmographic methods, Sjostrand (1963) found that about 78% of the blood displaced to the dependent parts of the body in the standing position is derived from the intrathoracic vascular compartments. The estimated quantity of blood present in the heart and the pulmonary circuit was thereby diminished by approximately 25%. These latter findings are in agreement with others (Lagerlof et al, 1954; Lewis et al, 1960; Weissler et al, 1957). The intrathoracic vessels therefore function as a reservoir. This blood store of the central circulation is especially important after a sudden assumption of the upright position when cardiac output temporarily exceeds venous return until the forced expansion of the capacity

vessels of the legs is completed. According to Sjostrand (1963), changes of intrathoracic blood volume are distributed between the pulmonary vessels and the heart in a ratio of about 3 to 1.

PULMONARY CIRCULATION

On assumption of the upright posture the intrathoracic circulatory pools are depleted by approximately 500 ml of blood and cardiac output, and hence total pulmonary flow, is reduced by approximately 30 %. While these points have already been discussed, it is necessary to scrutinize the effect of a change in body position on intravascular pressures as well as the redistribution of volume and flow within the pulmonary vascular bed. As early as 1887, Orth suggested that in the upright posture the pulmonary apex is anemic.

According to Bevegard et al. (1960) the pulmonary arterial pressure of 28/10 cm H_2O in recumbency falls to 20/7.5 cm H_2O and the mean pressure from 17 cm H_2O to 12 cm H_2O in the upright position. Calculation of the changes of pulmonary blood flow resistance during the behavior of left atrial pressures are scarce. Data of Lagerlof et al. (1951) suggest that it about doubles when changing from the recumbent to the erect position.

When comparing the length of the fluid column given by the vertical length of the lungs (15 to 25 cm) with the absolute pressures in the pulmonary vessels, we can safely assume from the principles outlined above that in the upright position the apical vessels are at best perfused during a short period of systole only. It is true that the intrathoracic pressure falls when moving between a recumbent and upright position. This pressure decrease cannot, however, compensate for the intravascular pressure changes because the capillary walls are exposed to alveolar pressure (Duomarco and Rimini, 1962) which on average is identical to atmospheric pressure, regardless of posture. Therefore, for all practical purposes the capillary bed at the apex is collapsed in the erect posture. While the greater portion of the volume, displaced from the upper lobes, is drained into

the leg veins, some of it is pooled in the basal lung area according to the hydrostatic pressure gradient.

Lung Volumes

There are three reasons why Total Lung Capacities (TLC) and other lung volumes should change in recumbency: 1) change in the position of the diaphragm, 2) change in the dimensions of the chest wall, and 3) change in the volume of blood in the lungs. Briscoe (1965) and Wade and Gilson (1951) found radiologic signs of elevation of the diaphragm in the supine position. The transverse and anteroposterior diameters of the chest increase when supine (Hamilton and Morgan, 1931). If the rise in the diaphragm when supine reduced lung volume more than the increased chest girth augmented it, then this alone would be enough to explain the reduced volumes in recumbency. However, most observers invoke the third mechanism, increase in the volume of blood in the chest, to explain the reduced volumes in the supine position, since VC was not appreciably less in the supine position than in the erect position while tourniquets were applied to the limbs (Hamilton and Morgan, 1931).

Sjostrand (1965) measured both the Functional Residual Capacity (FRC) and the volume of the trunk in a corset which functioned as a plethysmograph. He also measured chest circumference with a pneumogram. After tilting six subjects from a supine to an erect position, he observed the usual lung volume changes, notably mean increases of 335 (VC), 470 (TLC), and 725 ml (FRC), in the erect posture. However, the resting trunk volume measured by the corset plethysmograph only increased by 285 ml. Therefore, a large part of the increase in FRC (725-285=440ml), is due to a decrease in the volume of nongaseous material in the chest, presumably blood. Likewise the increase in TLC in the erect posture is almost entirely accounted for by the decreased volume of blood in the chest; the external volume of the trunk measured in the position of maximum inspiration is only 30 ml more than when supine. It is now accepted that the reduced

lung volumes in the supine position are the result of an increase in blood volume in the thoracic cavity.

CHANGING BODY POSITION AT REST

The effect on Dlco of changing from a seated to a supine position has been well documented (Bates, 1956; Hirasuna and Gorin, 1981; Stam et al, 1991). With the increase in Dlco being attributed predominantly to an increase in Vc with an associated minor increase in Dm. It is possible to account for the different changes in Vc and Dm from what we have explained previously about the effects of gravity on the pulmonary capillaries. In the upright lung, gravity causes lower vascular pressures at the apex, with the result that the apical blood flow is small and capillary filling is very uneven (Glazier, 1969). With the increasing distance down the lung, blood flow increases and so does the number of open capillaries. This recruitment increases the surface area of the blood-gas barrier (and hence Dm) considerably. By contrast, distension of already open capillaries through changes in their shape (West et al, 1991) and unfolding of the convoluted alveolar-capillary membrane (Mazzone, 1978) has only a minor effect on Dm.

In the transition from the sitting to the supine position, there is an immediate increase in pulmonary capillary blood flow as venous return to the thorax increases (Hirasuna and Gorin, 1981). The resulting rise in pulmonary vascular pressures causes some additional recruitment and distension of capillaries. However, the capillaries in the upper regions of the lung are not fully recruited because of the relatively low vascular pressure there. Thus although Vc is substantially elevated, the rise in Dm is small (Chang et al, 1992; Prisk et al, 1993; Stam et al, 1991).

The effect on Dm of changing body position is still the matter of some debate. Chang et al. (1992) showed a 6% significant increase in Dm upon assuming a supine position in a group of males under forty years of age. This result is supported by Prisk et al. (1993) who also noted a

significant 7% increase in Dm with a corresponding 30% increase in Vc, in seven male subjects in the supine compared with the seated position. Conversely, other researchers have found no significant difference (Hirasuna and Gorin, 1981; Lewis, 1958) and even Chang's older group (>40 years) showed no significant change in Dm after lying down. Initial work by Lewis et al. (1958) failed to show a significant change in Dm. All subjects did however display a reduced value (mean -21%) in the supine position, with only the small sample size (n=4) preventing any significance from being achieved. More recently, Hirasuna and Gorin (1981) detailed the effect of prolonged recumbency on Dm. They found that despite an initial mean 49% increase 5 minutes post-position change, and proceeding 18.3% per hour decrease in Vc, that Dm fluctuated above and below the pre-supine seated measure for two hours without ever reaching a significantly different level.

POST-EXERCISE RECOVERY POSITION

Recent investigations have attempted to explain the effect of post-exercise measurement position on pulmonary diffusing capacity (Hanel et al, 1997; Stewart et al, 1997). Stewart et al. (1997) showed that after one hour of recovery in a supine position Dlco and Dm were both significantly increased (14 and 16%, respectively), while Vc showed no statistically significant change from the pre-exercise seated value. Confirming previous research, one hour of seated recovery resulted in a significant decrease in Dlco (-10%), Dm (-10%), and Vc (-11%). Methodologically the supine values are not true reflections of an exercise interaction alone as the baseline Dlco measurement was conducted in a seated position. It therefore appears that the change in body position had a larger impact on Dlco, Dm and Vc than the exercise bout.

Hanel et al. (1997) investigating the redistribution of blood volume from the central vascular bed to more distal regions following exercise, reported a decrease in Dlco in both seated

and supine positions (6 and 12%, respectively). A corresponding change in thoracic-to-thigh electrical impedance ratio (+14%), a decrease in thoracic (-7%) and an increase in thigh blood volume (+3%), in the seated position only, supported the authors hypothesis explaining the post-exercise decrease in Dlco. There were also methodological problems associated with Hanel's work. Only 15 minutes of stabilization existed between seated and supine measurements which were conducted in the same testing session, despite all the recovery being done in a supine position.

SUMMARY

Dlco is impaired after exercise of various duration and intensities (Caillaud et al, 1995; Manier et al, 1993; Sharratt et al, 1996; Stewart et al, 1997). The post-exercise restriction of Dlco persists for at least 6 hours (Sheel, 1995); and the pre-exercise Dlco is not re-established for 1-2 days (Rasmussen et al, 1998; 1992; Sheel, 1995). The post-exercise reduction reflects a decrease in both Dm and Vc. Several mechanisms have been suggested to explain the impairment: (1) a reduced central blood volume (Hanel et al, 1994, 1997); (2) acute subclinical interstitial pulmonary edema (Caillaud et al, 1995); and/or (3) microvascular injury to the alveolar-capillary membrane.

A change in body position from erect to supine results in an increased venous return, cardiac output and therefore total pulmonary flow is enhanced by approximately 30% (Sjostrand, 1963). If the post-exercise decrease in Dlco and Dm was a function primarily of a relocation of blood into the periphery causing a decrease in Vc, then by placing the subject in a supine position the enhanced venous return post-exercise should compensate for the pooling and return Vc to baseline supine levels, resulting in a similar change in Dlco and Dm, compared with the erect post-exercise levels which would remain depressed.

Dm is affected by two factors: the surface area of the lung which is actively perfused; and inversely by the thickness of the alveolar-capillary membrane. Only the surface area available for diffusion is affected by the other component of Dlco, Vc. Thus if some other physiological occurrence is causing Dm to be reduced via increasing the thickness of the membrane component i.e. acute pulmonary edema, thereby assisting Vc in decreasing Dlco in the erect position, then the supine post-exercise position which returns Vc to baseline levels, will not result in a similar change in Dm. This in turn will still have a negative effect on Dlco, the overall magnitude of which will be a balance between the decreased Dm and the new value for Vc.

APPENDIX B.

EFFECT OF CARBOXYHEMOGLOBIN ON REPEATED MEASUREMENTS OF PULMONARY DIFFUSING CAPACITY

The presence of carboxyhemoglobin (COHb) in the blood impedes the transfer of carbon monoxide from the alveolar gas to the red blood cell in the pulmonary capillaries during the measurement of pulmonary diffusing capacity with carbon monoxide (Dlco) (Ogilvie et al, 1975). This is due to the back pressure of carbon monoxide in the pulmonary capillaries reducing the driving pressure for carbon monoxide across the alveolar-capillary membrane. The purpose of this pilot study was to ascertain the effect of carboxyhemoglobin build-up on the measurement of Dlco at the time intervals utilized in the parent study.

Methodology

One healthy non-smoking male subject was recruited. The subject displayed normal pulmonary function and had no history of cardiovascular or respiratory disease. The experimental protocol followed was identical to that of the main study (page 5), with the exception that no exercise was performed. Approximately 5 ml of blood was obtained by an indwelling catheter placed in the upper forearm. Samples were collected immediately prior to and after the performance of four (allowing for partitioning) single breath Dlco procedures. Analysis of hemoglobin concentration and COHb saturation were performed with a CO-oximeter sprectrophotometer using three wavelengths to determine concentrations of reduced hemoglobin (Hb), oxyhemoglobin (O_2Hb), and carboxyhemoglobin (COHb), from which the saturation of carboxyhemoglobin (% COHb) is calculated by the equation:

% COHb = COHb/(Hb + O_2Hb + COHb) X 100

Dlco was obtained as detailed in the parent study.

Results

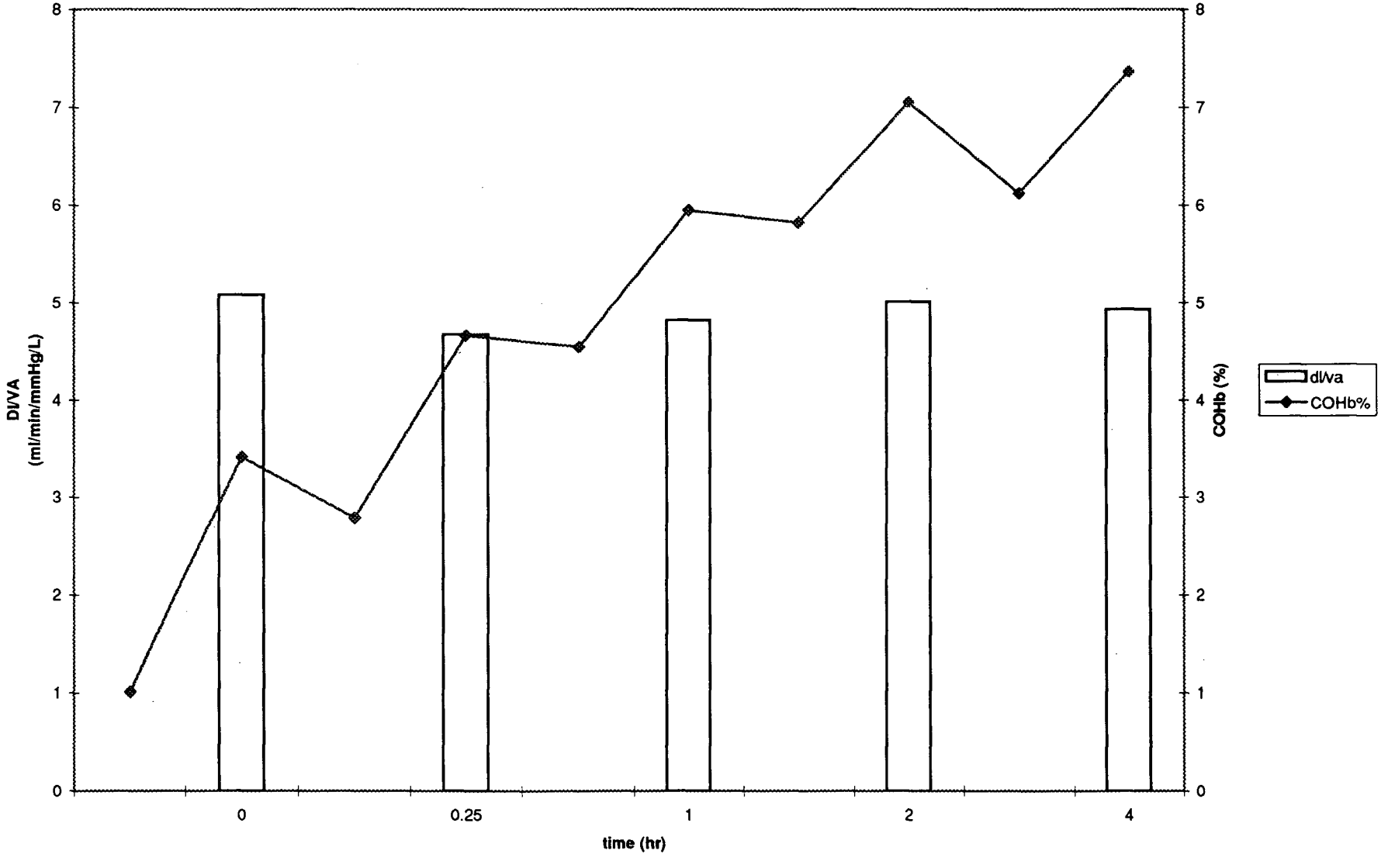
Table 1. COHb levels (%)

TIME (24 hr)	1150	1210	1250	1320	1340	1400	1440	1500	1640	1700
COHb (%)	1.0	3.4	2.8	4.7	4.5	5.9	5.8	7.1	6.1	7.4

Table 2. Dlco (ml. min^{-1}. $mmHg^{-1}$), corrected for alveolar volume, during rest (BASE) and following no exercise.

TIME	BASE	15 min	1 hr	2 hrs	4 hrs
24 hr	1200	1305	1350	1450	1650
Without Exercise	5.08	4.67	4.82	5.01	4.93

Figure 1. Carboxyhemoglobin saturation levels during repeated measurements of pulmonary diffusing capacity



Discussion

This pilot study confirmed that the degree of saturation of COHb increases in the blood stream during repeated measurements of Dlco (Table 1). A 1% increase in COHb saturation has been suggested to reduce Dlco, calculated without adjustment for COHb, by approximately 1% of the observed baseline value (Mohsenifar and Tashkin, 1979).

Each set of Dlco measurements resulted in an increase in COHb saturation ranging from 1.3 to 2.4%, while clearance between measurement periods ranged from 0.004-0.016% per minute. During this period of increasing COHb saturation, Dlco was seen to fluctuate around the baseline level. Hanel et al. (1994) found no significant effect on Dlco of repeated measurement procedures over a six hour time span. While the effect on Dlco of non-smoking healthy subjects has been termed "inconsequential" (Mohsenifar and Tashkin, 1979). It is difficult to draw conclusions from a study with a sample size of only one, but increasing levels of COHb appeared to have minimal effect on the repeated Dlco values. Therefore, based on previous findings and the results of this pilot study, Dlco was not adjusted for COHb levels in the parent study.

APPENDIX C

RAW DATA ANALYSIS

Table 1. Pulmonary diffusing capacity for carbon monoxide (mL/min/mmHg) during rest (BASE) and following maximal exercise, position data.

POSITION	BASE	15 min	1 hr	2 hrs	4 hrs
SEATED (n=10)	39.65 (7.83)	41.85 (9.88)	33.85 (8.24)	33.87 (7.64)	33.61 (7.01)
SUPINE (n=10)	41.57 (7.91)	42.90 (6.93)	36.61 (6.28)	36.19 (4.72)	36.10 (4.90)
MEAN (± SD)	40.61 (7.72)	42.37 (8.32)	35.23* (7.27)	35.03* (6.30)	34.85* (6.03)

Values are means (± SD).
* significantly different compared with baseline (P<0.05).

Table 2. Dlco ANOVA (5 X 2) RM

	SS	df	MS	F	sign. F
TIME	1032.52	4	258.13	35.42	<0.001
WITHIN + RESIDUAL	262.32	36	7.29		
POSITION	111.53	1	111.53	1.48	0.255
WITHIN + RESIDUAL	678.51	9	75.39		
INTERACTION	8.79	4	2.20	0.37	0.831
WITHIN + RESIDUAL	215.82	36	6.00		

Table 3. Membrane diffusing capacity (mL/min/mmHg) during rest (BASE) and following maximal exercise, position data.

POSITION	BASE	15 min	1 hr	2 hrs	4 hrs
SEATED (n=10)	51.31 (8.22)	55.58 (12.49)	43.16 (9.94)	44.62 (10.46)	43.54 (8.50)
SUPINE (n=10)	53.47 (11.09)	59.71 (15.82)	48.64 (12.65)	47.70 (6.68)	47.17 (6.64)
MEAN (± SD)	52.39 (9.56)	57.64 (14.03)	45.9* (11.43)	46.16* (8.68)	45.35* (7.65)

Values are means (± SD).
* significantly different compared with baseline (P<0.05).

Table 4. Dm ANOVA (5 X 2) RM

	SS	df	MS	F	sign. F
TIME	2319.76	4	579.94	13.75	<0.001
WITHIN + RESIDUAL	1517.87	36	42.16		
POSITION	341.00	1	341.00	3.23	0.106
WITHIN + RESIDUAL	950.47	9	105.61		
INTERACTION	30.66	4	7.66	0.21	0.932
WITHIN + RESIDUAL	1324.62	36	36.79		

Table 5. Pulmonary capillary blood volume (mL) during rest (BASE) and following maximal exercise, position data.

POSITION	BASE	15 min	1 hr	2 hrs	4 hrs
SEATED (n=10)	109.46 (40.05)	102.73 (31.27)	95.07 (29.86)	87.57 (25.80)	93.80 (28.44)
SUPINE (n=10)	111.50 (31.72)	106.83 (50.93)	92.27 (16.36)	87.19 (17.18)	89.04 (17.34)
MEAN (± SD)	110.48 (35.18)	104.78 (41.18)	93.67* (23.48)	87.38* (21.33)	91.42* (23.05)

Values are means (± SD).
* significantly different compared with baseline (P<0.05).

Table 6. Vc ANOVA (5 X 2) RM

	SS	df	MS	F	sign. F
TIME	7510.76	4	1877.69	4.12	0.008
WITHIN + RESIDUAL	16422.28	36	456.17		
POSITION	3.22	1	3.22	0.00	0.971
WITHIN + RESIDUAL	20437.43	9	2270.83		
INTERACTION	254.79	4	63.70	0.14	0.967
WITHIN + RESIDUAL	16666.52	36	462.96		

Table 7. Alveolar volume (V_A) (L) during rest (BASE) and following maximal exercise, position data.

POSITION	BASE	15 min	1 hr	2 hrs	4 hrs
SEATED (n=10)	7.71 (1.06)	7.71 (0.97)	7.62 (1.04)	7.53 (1.15)	7.63 (1.16)
SUPINE (n=10)	7.21 (1.18)	7.63 (1.13)	7.47 (1.26)	7.41 (1.17)	7.19 (1.26)
MEAN (± SD)	7.46 (1.12)	7.67 (1.02)	7.55 (1.12)	7.47 (1.13)	7.41 (1.20)

Values are means (± SD).

Table 8. V_A ANOVA (5 X 2) RM

	SS	df	MS	F	sign. F
TIME	0.82	4	0.21	1.18	0.338
WITHIN + RESIDUAL	6.31	36	0.18		
POSITION	1.68	1	1.68	5.93	0.038
WITHIN + RESIDUAL	2.55	9	0.28		
INTERACTION	0.77	4	0.19	1.31	0.285
WITHIN + RESIDUAL	5.30	36	0.15		