0195-9131/91/2312-1353$3.00/0
MEDICINE AND SCIENCE IN SPORTS AND EXERCISE

Vol. 23, No. 12
Printed in U.S.A.

Red blood cell pulmonary capillary transit time during exercise in athletes

GORDON L. WARREN, KIRK J. CURETON, WAYNE F. MIDDENDORF, CHESTER A. RAY, and JULIE A. WARREN

Exercise Physiology Laboratory, The University of Georgia, Athens, GA 30602

ABSTRACT

WARREN, G. L., K. J. CURETON, W. F. MIDDENDORF, C. A. RAY, and J. A. WARREN. Red blood cell pulmonary capillary transit time during exercise in athletes. *Med. Sci. Sports Exerc.*, Vol. 23, No. 12, pp. 1353–1361, 1991. The purpose of this study was to test the hypothesis that the exercise-induced hypoxemia observed in endurance athletes is due to a reduction in the mean red blood cell pulmonary capillary transit time consequent to a plateau in pulmonary capillary blood volume (Vc) as exercise intensity progresses from moderate to heavy levels. Measurements of Vc, mean transit time, arterial O_2 tension (PaO_2), and end tidal-arterial O_2 tension difference ($AaDO_2$) were made in 16 subjects (mean maximal oxygen uptake ($\dot{V}O_{2max}$) = 4.90 $l \cdot min^{-1}$) at rest and during five cycle exercise bouts designed to elicit 55, 65, 75, 85, and 95% $\dot{V}O_{2max}$. Mean PaO_2 fell from 101 mm Hg at rest to 85 mm Hg during heavy exercise. Mean $AaDO_2$ increased linearly from one stage to the next and at the highest work rate equaled 22.3 mm Hg. Mean Vc failed to plateau with increasing exercise intensity and increased on average by 16 ml from one stage to the next. Mean transit time, on average, dropped from 1.05 s at rest to 0.46 s at the lowest work rate. Mean transit time did not decrease further with increasing exercise intensity (range, 0.42–0.46 s). We conclude that, under the conditions of this study, the $AaDO_2$ increases and PaO_2 decreases observed in endurance athletes during exercise of increasing intensity is not caused by a plateau in Vc and a consequent reduction in mean transit time.

ARTERIAL DESATURATION, DIFFUSION LIMITATION, EXERCISE, GAS EXCHANGE, HYPOXEMIA, PULMONARY CAPILLARY BLOOD VOLUME, PULMONARY FUNCTION

Many highly trained endurance atheletes exhibit exercise-induced hypoxemia during heavy exercise (9,21,26,28,33–35). Exercise-induced hypoxemia in these athletes may occur at an exercise intensity as low as 70% of maximal oxygen uptake ($\dot{V}O_{2max}$) and becomes more pronounced in heavier exercise (27). As exercise intensity increases from moderate to heavy levels, arterial O_2 tension (PaO_2) may fall to 60–80 mm Hg (9,33,34) while arterial hemoglobin saturation (HbO_2%) may drop to 90% or below (21,26,28,35).

The mechanism primarily responsible for the decline in PaO_2 and HbO_2% with increasing exercise intensity remains undetermined. The principal cause of exercise-induced hypoxemia in the endurance athlete has been speculated to be a pulmonary diffusion limitation (7,29). It is hypothesized that pulmonary capillary blood volume (Vc) expands during exercise of increasing intensity until it reaches its morphological limit of 210–220 ml at a cardiac output ($\dot{Q}$) of about 25 $l \cdot min^{-1}$ or a $\dot{V}O_2$ of approximately 3.5 $l \cdot min^{-1}$ (Fig. 1). At this intensity of exercise, the mean red blood cell transit time through the pulmonary capillary bed (equal to Vc divided by $\dot{Q}$) is approximately 0.5 s. This mean transit time is well above the minimum time (0.35–0.40 s) thought to be required for complete O_2 equilibration between alveolar gas and end-capillary blood (10,14). At higher exercise intensities, $\dot{Q}$ continues to increase but it is hypothesized that Vc does not. The plateau in Vc would result in a more rapid decline in mean transit time and an increase in the percentage of red blood cells (RBC) passing through the pulmonary capillary bed in 0.35–0.40 s or less.

However, no studies have reported definitive evidence for a plateau in Vc and a concomitant drop in mean transit time as exercise intensity progresses from moderate to heavy levels. The objective of this study was to measure Vc and mean transit time in highly trained endurance athletes during exercise of moderate to near-maximal intensities and to determine whether the increase in the alveolar-arterial O_2 tension differences ($AaDO_2$) and the decrease in PaO_2 with increasing exercise intensity are paralleled by a reduction in mean transit time.

METHODS

Subjects. Screening tests were conducted to identify athletes who would be most likely to exhibit exercise-induced hypoxemia during heavy exercise. The screening test consisted of a progressive, graded, maximal cycle ergometer test employing pulse oximetry (Novametrix 500 or Criticare 501+ oximeters). A total of 81

Submitted for publication July 1990.
Accepted for publication March 1991.

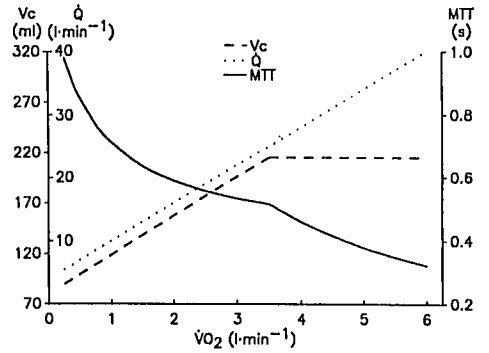

Figure 1—Concept of diffusion limitation in exercise-induced hypoxemia. Pulmonary capillary blood volume (Vc) and cardiac output ($\dot{Q}$) increase linearly with increasing exercise intensity up to a $\dot{Q}$ of about 25 $l \cdot min^{-1}$ or an oxygen uptake ($\dot{V}O_2$) of 3.5 $l \cdot min^{-1}$. At higher exercise intensities, $\dot{Q}$ continues to increase but Vc does not. This results in a more rapid decline in the mean red blood cell pulmonary capillary transit time (MTT), as $\dot{V}O_2$ exceeds 3.5 $l \cdot min^{-1}$.

TABLE 1. Physical characteristics and pulmonary function of the subjects at rest.

	Mean	Min-Max
Age (yr)	24.3	19–38
Height (m)	1.82	1.71–1.91
Mass (kg)	73.0	60.3–87.8
$\dot{V}O_{2max}$		
$(l \cdot min^{-1})$	4.90	4.09–5.53
$(ml \cdot kg^{-1} \cdot min^{-1})$	67.4	59.8–75.8
Min HbO_2 (%)*	90.6	87–96
FVC (l)	6.16	4.78–7.20
FEV_1		
$(l \cdot s^{-1})$	5.12	4.20–6.16
(%FVC)	83.2	73.7–94.6
PEFR $(l \cdot s^{-1})$	10.82	9.16–13.01
MVV $(l \cdot min^{-1})$	188	147–235
DLCO $(ml \cdot min^{-1} \cdot mm\ Hg^{-1})$	46.3	33.8–58.9

FVC = forced vital capacity; FEV_1 = forced expiratory volume at 1 s; PEFR = peak expiratory flow rate; MVV = maximal voluntary ventilation.
* Minimum pulse oximetric estimate of HbO_2% observed during the preliminary screening test.

potential subjects were screened for exercise-induced hypoxemia. Males and females known to have a $\dot{V}O_{2max}$ of at least 65 and 55 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively, were screened. In addition, individuals running more than 64 km per week or cycling at least 240 km per week were also tested. Selection criteria included: 1) a pulse oximetric estimate of HbO_2% $\leq$ 90% during heavy exercise and/or 2) a $\dot{V}O_{2max} \geq$ 65 $ml \cdot kg^{-1} \cdot min^{-1}$.

Sixteen males were selected to participate in this study. Nine of the 16 exhibited a HbO_2% estimate equal to or less than 90% for 30 s or more on the screening test. However, the mean HbO_2% measured by CO-oximetry during the experiment for these nine subjects was not statistically different from that of the other seven. Because of this, all 16 subjects were treated as one group for data analysis purposes.

The physical characteristics and resting pulmonary function measures of the subjects are summarized in Table 1. Resting pulmonary function was for the most part normal, but two subjects had maximal voluntary ventilations slightly below 80% of values predicted by the equation of Kory et al. (20). For these two subjects, forced vital capacity, forced expiratory volume at 1 s, and peak expiratory flow rate were in the normal range determined using the Michigan equations (24). All but two subjects had pulmonary diffusing capacities for carbon monoxide (DLCO) above that predicted by the Michigan equations (24).

Testing was conducted in accordance with the American College of Sports Medicine policy statement regarding the use of human subjects. All subjects were familiarized with the experimental protocol and gave written informed consent prior to testing. In addition, all subjects performed a practice session 1–3 d prior to the experiment. This was done to familiarize the subject with the DLCO and $\dot{Q}$ measurement procedures as well as to enable determination of test-retest reliability for these measurement techniques. The protocol for the practice session was a shortened version of the experimental protocol and involved measurements at rest and at work rates designed to elicit 65 and 85% $\dot{V}O_{2max}$. Also at this time, measurements of resting lung volumes and flow rates were made.

Experimental protocol. Testing was conducted at an altitude of 240 m, with a barometric pressure of 740–750 mm Hg. A discontinuous exercise protocol was employed with five 4-min bouts of cycle exercise on a Mijnhardt electronically braked cycle ergometer at intensities designed to elicit 55, 65, 75, 85, and 95% $\dot{V}O_{2max}$. The exercise bouts were performed in order of increasing exercise intensity. Prior to the work rate designed to elicit 55% $\dot{V}O_{2max}$, the subject rested for 15 min while seated on the ergometer, followed by 10 min of cycling at 100 W. There was 5 min of rest in between bouts (except for 10 min between the 100 W and 55% $\dot{V}O_{2max}$ bouts), thus making the protocol 1 h in length.

This protocol was repeated 1.5–2.0 h after completion of the first set of exercise bouts. During this second set of exercise bouts, the subject breathed an O_2:N_2 gas mixture (%O_2 = 90–100%) for 3 and 5 min prior to the measurement of DLCO during exercise and at rest, respectively.

Experimental measures. Expired gas analysis was performed utilizing a Medical Graphics Corporation (MGC) 2001 system. Cardiorespiratory measures including minute expired ventilation ($\dot{V}E$), CO_2 production ($\dot{V}CO_2$), $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$, $\dot{V}E/\dot{V}O_2$, end-tidal CO_2 tension ($PETCO_2$), and end-tidal O_2 tension ($PETO_2$) were averaged over 1-min intervals, and the values from the last min of rest and each exercise bout were used in the data analysis. Mean alveolar O_2 tension (PAO_2) was estimated using the alveolar air equation and also from $PETO_2$. $PETO_2$ was used to estimate PAO_2 because volume-averaged expired PAO_2 was not measured and

because the ideal PAO_2 calculated using the alveolar air equation has been found to overestimate measured expired PAO_2 during heavy exercise (1). The MGC 2001 was calibrated immediately prior to each test session. The pneumotachometer was calibrated using a 3-l syringe and the O_2 and CO_2 analyzers were calibrated using precision-grade medical gases.

The severity of hypoxemia during the first set of exercise bouts was assessed using arterial blood gas analysis. After application of a local anesthetic (lidocaine), a 20-gauge arterial catheter was inserted into the radial artery of the left arm. Arterial blood samples were withdrawn anaerobically into heparinized 3-ml syringes during the last 30 s of each exercise bout and stored on ice until analyzed. In addition, three resting samples were taken, one each at 10, 5, and 1 min prior to the start of the 100-W bout. Blood gas values from the three resting samples were averaged for use in subsequent data analysis. The blood samples were assayed for PaO_2, arterial CO_2 tension ($PaCO_2$), hemoglobin concentration ([Hb]), carboxyhemoglobin (HbCO), and HbO_2. A Ciba Corning 278 blood gas system was used to measure PaO_2 and $PaCO_2$. [Hb] and percentages of HbO_2 and HbCO were determined using a Corning 2500 CO-oximeter. Arterial O_2 content (CaO_2) was calculated using the equation: $CaO_2\ (ml \cdot dl^{-1}) = 0.0135\ (HbO_2\%)\ [Hb] + 0.0031\ PaO_2$. Two- and one-point calibrations were performed on the Ciba Corning 278 system every 2 h and 30 min, respectively. Liquid control samples (Ciba Corning Certain Advance) were assayed every 8 h to check the blood-gas correction factor. Three control samples were used with PO_2s in the following ranges: 50–60, 95–105, and 140–160 mm Hg. Hemoglobin slope calibration of the CO-oximeter was performed on a daily basis and checked every 8 h using three control solutions (Ciba Corning Certain Advance) of known [Hb], $HbO_2\%$, and $HbCO_2\%$. In addition, the zero-point of the CO-oximeter was reset every 45 min.

A correction was applied to PaO_2 that accounted for the metabolic events (O_2 consumption, CO_2 production, and pH reduction) occurring in the blood in the time between withdrawal and analysis (19). The mean (±SD) time between withdrawal and analysis was 16.3 (±8.3) min. The mean correction applied to PaO_2 was +0.9 mm Hg. Following this correction, PaO_2 was corrected to sublingual temperature (19). Sublingual temperature was measured with a thermistor probe, immediately following each exercise bout, and used as an estimate of arterial temperature during the last 30 s of the previous bout. Sublingual temperature has been found to approximate esophageal temperature at rest and during short-term transient exercise (deviation range of −0.18 to +0.12 °C with a time lag of 1–3 min) (6,11,22,32). This measurement site was chosen over rectal and esophageal sites for two reasons. First, rectal temperature typically overestimates esophageal temperature by 0.2–0.4 °C and is slow to respond to changes in blood/core temperature (22,32). Second, it was concluded that the increased accuracy of using esophageal temperature (and therefore, a nasoesophageal catheter) would not have offset the discomfort and possible negative effect on ventilatory patterns. In using sublingual as opposed to esophageal temperature, PaO_2 error would not be expected to exceed ±1.1%.

In addition, the blood of each athlete was analyzed for any hemoglobin abnormalities that might have resulted in arterial hemoglobin desaturation. A 10-ml arterial blood sample was drawn and studied by the use of an automated cell counter to determine red cell parameters, by isoelectrofocusing; and Hb A_2 quantitation was done by microcolumn chromatography. These procedures were used to exclude β-thalassemia or α-thalassemia and an abnormal hemoglobin.

Cardiac output was determined at rest and during the first set of exercise bouts by using echocardiography (Hewlett Packard 77020AC ultrasound system) and the technique recommended by Christie et al. (4). This technique was selected because it is noninvasive, yet yields estimates of $\dot{Q}$ during strenuous upright cycle exercise that are comparable in accuracy to the thermodilution and direct Fick methods (4). This echocardiographic technique measures ascending aortic blood flow velocity from the suprasternal notch using continuous-wave Doppler echocardiography (HP 21221A nonimaging 45° off-axis transducer operating at 1.9 MHz with a focal depth of 5 cm) and aortic anular diameter from a left parasternal long-axis view of the aortic valve using two-dimensional echocardiography (HP 21200A phased-array transducer operating at 2.5 mHz with a focal depth of 2–14 cm). Aortic anular diameter was measured while the subject was at rest on the cycle ergometer prior to the first set of exercise bouts. Five diameter measurements made at the level of the insertion point of the aortic valve leaflets were averaged and used to calculate the effective cross-sectional flow area (flow area = π(diameter/2)^2). Both the aortic anular diameter and the systolic blood flow velocity integral were determined from videotaped recordings by using a microcomputer-assisted planimeter. The Doppler waveforms chosen for analysis were those with the highest peak velocities and clear distinct waveforms. Heart rate (HR) was measured using a 3-lead ECG (Lead II) configuration that was input into the ultrasound unit. Estimates of $\dot{Q}$ represent the average of five cardiac cycles from the last 30 s of rest and each exercise bout.

To indirectly confirm the validity of the echocardiographic $\dot{Q}$ measurements, the $\dot{Q}/\dot{V}O_2$ relation was examined using data collected at rest and at each of the exercise intensities. The relation was: $\dot{Q}\ (l \cdot min^{-1}) = 4.62 + 5.82\ VO$ ($r = 0.97$, SEE = 2.06), which is very

similar to those reported in the literature for traditional methods (13). In addition, the test-retest reliability of measurements made at rest and at 65 and 85% $\dot{V}O_{2max}$ was determined on 12 subjects on two separate days. The overall intra- and interclass correlation coefficients (3) between the two trials equaled 0.88 and 0.99, respectively. The overall coefficient of variation was 5.6%, with the greatest variability coming from measurements made at rest (c.v. = 10.2%). The above observations suggest that the echocardiographic technique was valid and reliable for $\dot{Q}$ measurement in this study's highly trained subjects.

The membrane diffusing capacity (Dm) and Vc were estimated from measurements of DLCO by using the method of Roughton and Forster (30). The single-breath technique of measuring DLCO was selected over the steady-state method because it is less susceptible to uneven ventilation and ventilation/perfusion inequalities. The DLCO measurement was performed by using a P. K. Morgan Transfer Test Auto-Link unit. The spirometer and gas analyzers (CO, He, and O_2) in this unit were calibrated prior to each set of exercise bouts. At rest and in the final 30 s of each work bout, the subject was connected to a spirometer with a balloon-in-the-box system. The subject inhaled a maximum breath (approximately 90% forced vital capacity) from residual volume of a gas containing 0.3% CO, 10% He, 21% O_2, and 68.7% N_2, and then held his breath for 10 s. The actual breath-hold time was calculated as the time from one-third inspiration to the mid-point of the expired sample. During exhalation, a 900-ml alveolar sample was collected and analyzed for CO, He, and O_2 concentrations.

After DLCO had been measured at rest and at each work rate with the 21% O_2 gas mixture, the subject rested for 1.5–2.0 h. Measurements of DLCO were then made at rest and at each work rate by using a gas mixture of 0.3% CO, 10% He, and 89.7% O_2. For the 3 min prior to each DLCO maneuver during exercise, the subject breathed a gas mixture containing 90–100% O_2 with the remaining balance being N_2. While at rest, the subject breathed this mixture for 5 min prior to the maneuver.

From the measurements of DLCO at the two different inspired O_2 tensions, Vc and Dm were calculated. This required solution of two simultaneous equations of the form: $1/DLCO = 1/Dm + 1/(Vc \cdot \theta)$, where θ is the reaction rate of CO with hemoglobin. Solution is possible because θ varies with inspired O_2 tension. Specifically, $1/\theta$ is related to the mean O_2 tension in the plasma of the pulmonary capillaries ($PcapO_2$) ($1/\theta = (0.34 + 0.006\ PcapO_2)/[([Hb]/15)\ (1 - HbCO\%/100)]$ mmHg·min·ml blood·ml CO^{-1}) (5). Because pulmonary capillary [Hb] is unknown, arterial [Hb] was used in this calculation. Using arterial [Hb] values might affect the estimation of absolute values for Vc and Dm, but between-work rate comparisons should not be affected. $PcapO_2$ was estimated from PAO_2 and O_2 uptake occurring during the breath-hold (5). In calculating Vc and Dm, it was assumed that these two parameters were the same during the DLCO measurements at low and high inspired O_2 tensions. Since $\dot{Q}$ may (12) or may not (2) be reduced during high $\%O_2$ breathing, it is possible that estimates of Vc and Dm could be slightly low and high, respectively. However, these inaccuracies might be offset by the effect of the Valsalva maneuver. Since the Valsalva maneuver is more likely to occur during the DLCO maneuver made at 21% O_2, this would tend to produce an overestimation of Vc and underestimation of Dm.

DLCO was corrected for carbon monoxide back pressure in the pulmonary capillaries. The pulmonary capillary CO tension was estimated from the Haldane relation ($PCO = [(HbCO\%)\ (PO_2)]/[210\ (HbO_2\%)]$) (25). Corrections for the effect of [Hb] and HbCO on the determination of $1/\theta$ were applied as suggested by Cotes (5). Arterial [Hb] and HbCO% were measured at rest and each exercise intensity during the first set of exercise bouts. It was assumed that there was no difference in these measures between the two sets of exercise bouts. This assumption was tested in two subjects. Arterial [Hb] and HbCO% differed by no more than 0.3 $g \cdot dl^{-1}$ and 0.3%, respectively, between the two sets of exercise bouts.

Test-retest reliability for the Vc/Dm measurement technique was determined for measurements made at rest and during exercise designed to elicit 65 and 85% $\dot{V}O_{2max}$ on 16 subjects on two separate days. For Vc, the overall intra- and interclass correlation coefficients between the two trials were 0.74 and 0.91, respectively. The coefficients of variation for Vc were essentially the same at rest and at the two work rates (8.4–8.5%). For Dm, the overall intra- and interclass correlation coefficients between the two trials were 0.64 and 0.42, respectively. The overall coefficient of variation for Dm was 22.0%, ranging from 15.1 to 28.0% at higher and lower work rates, respectively.

Mean transit time was calculated by dividing Vc by $\dot{Q}$. This calculation ignores the existence of a right-to-left shunt, so the mean transit time estimates could be systematically low by 1–2%. Test-retest reliability for the mean transit time calculation was determined for measurements made at rest and during exercise designed to elicit 65 and 85% $\dot{V}O_{2max}$ on 12 subjects on two separate days. The interclass correlation coefficient between the two trials was 0.96. The overall intraclass correlation coefficient was 0.89. Intra-class r determined during exercise (0.77–0.95) were similar to that determined at rest (0.94). The coefficient of variation was 11.4% at rest but improved with increasing exercise intensity (8.1% and 4.7% at 65 and 85% $\dot{V}O_{2max}$, respectively).

Statistical analysis. The significance of differences among means for the measured and calculated variables at rest and during exercise was evaluated using a one-way ANOVA with repeated measures. When significant differences were found, single-degree-of-freedom contrasts were performed to determine means that were significantly different. A one-way ANOVA was used to determine the proportion of variance in $AaDO_2$ and PaO_2 explained by the variance in mean transit time. Because the variance in mean transit time explained a significant proportion of the variance in $AaDO_2$, change-point linear regression (18) was employed to determine the minimum mean transit time below which a marked widening in $AaDO_2$ occurred. With the exception of the change-point linear regression, all analyses were performed using PC-SAS (SAS Institute, Cary, NC). Change-point linear regression was performed using a BASIC program provided by Jones and Molitoris (18). An alpha level of 0.05 was used for all tests of significance.

RESULTS

In Table 2, the mean physiological responses at rest and during exercise designed to elicit 55, 65, 75, 85, and 95% $\dot{V}O_{2max}$ are presented. The mean actual $\%\dot{V}O_{2max}$ elicited by the five work rates was less than that predicted from work rates utilized. This difference was only 2.0% at the lowest work rate but increased to 6.9% at the work rate designed to elicit 95% $\dot{V}O_{2max}$. However, mean HR at the highest work rate averaged 184 beats·min^{-1}, which was 99.5% of the mean maximal HR recorded during the preliminary screening tests.

TABLE 2. Mean (SE) physiological responses at selected percentages of $\dot{V}O_{2max}$.

		$\%\dot{V}O_{2max}$				
	Rest	55	65	75	85	95
$\dot{V}O_2$ (l·min^{-1})	0.42	2.60	3.02	3.50	3.94	4.32
	(0.03)	(0.09)	(0.08)	(0.10)	(0.11)	(0.12)
Actual $\%\dot{V}O_{2max}$	—	53.0	61.5	71.4	80.6	88.1
		(1.1)	(1.0)	(1.3)	(1.4)	(1.2)
$\dot{V}CO_2$ (l·min^{-1})	0.37	2.47	2.86	3.41	3.99	4.55
	(0.02)	(0.09)	(0.07)	(0.11)	(0.10)	(0.14)
$\dot{V}E$ (l·min^{-1})	16.4	66.3	76.8	93.1	115.7	142.3
	(1.1)	(2.1)	(2.2)	(3.3)	(4.4)	(4.8)
$\dot{V}E/\dot{V}O_2$	41.0	25.6*	25.5*	26.7	29.4	33.1
	(3.0)	(0.6)	(0.5)	(0.7)	(0.9)	(1.0)
$\dot{V}E/\dot{V}CO_2$	44.8	27.0*	26.9*	27.3*	28.9	31.3
	(1.7)	(0.5)	(0.5)	(0.6)	(0.7)	(0.8)
PAO_2 (mm Hg)						
End-tidal	105.1*	98.5†	98.8†	101.1	104.8*	109.4
	(1.8)	(1.0)	(0.8)	(0.9)	(0.9)	(0.7)
Ideal	105.2*	105.0*	105.8*	107.6	110.1	114.0
	(1.4)	(0.8)	(0.7)	(0.8)	(0.9)	(0.9)
$PETCO_2$ (mm Hg)	38.1*	45.5†	45.5†	44.2	42.4	39.1*
	(1.0)	(0.8)	(0.8)	(0.2)	(0.9)	(0.7)
$PaCO_2$ (mm Hg)	36.7	38.9	38.2	37.3	36.0	33.1
	(0.6)	(0.6)	(0.6)	(0.6)	(0.7)	(0.8)
HR (beats·min^{-1})	62	134	148	162	175	184
	(2.3)	(2.7)	(2.4)	(2.1)	(2.3)	(2.4)
Temperature (°C)	37.0*	36.8*	37.0*	37.1†	37.2†§	37.3§
	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)

Values with the same symbol are not significantly different.

Figures 2 and 3 depict the results of the arterial blood analyses made at rest and during exercise. The mean PaO_2 at rest (101.1 mm Hg) was elevated, probably as a result of apprehension about the upcoming exercise session. The lowest mean PaO_2 occurred at the second highest work rate (84.9 mm Hg) while the lowest mean $HbO_2\%$ occurred at the highest work rate (91.5%). Individual PaO_2s ranged from 70.9 to 100.2 mm Hg at the highest work rate, with two athletes between 70 and 79 mm Hg, nine between 80 and 89 mm Hg, and the remainder at 90 mm Hg or above. Individual $HbO_2\%$ values ranged from 90.3 to 92.5% at the highest work rate. Of the 4.0% mean drop in $HbO_2\%$ from rest to the highest work rate, 53% of the drop could be attributed to a mild hyperthermia (0.3 °C rise) and metabolic acidosis (drop in pH from 7.42 to 7.31), resulting in a rightward shift of the Hb:O_2 dissociation curve. Mean CaO_2 remained relatively constant over the five work rates (range, 19.8–20.0 ml·dl^{-1}). This occurred because progressive hemoconcentration acted to offset the drop in $HbO_2\%$.

Figure 4 illustrates the mean $PETO_2$-PaO_2 differences at rest and during exercise. The $PETO_2$-PaO_2 difference

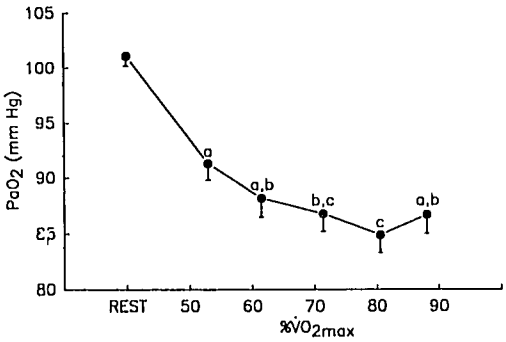

Figure 2—Arterial O_2 tension (PaO_2) responses at rest and the five exercise intensities. Values are means (±SE). Data points with the same letter are not significantly different.

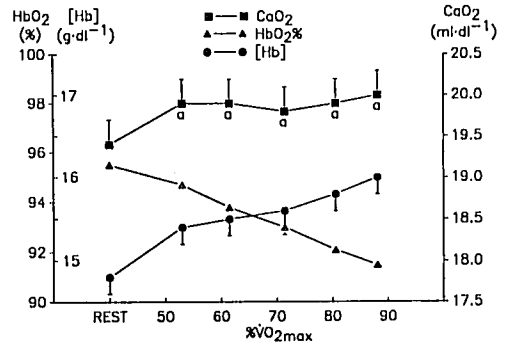

Figure 3—Arterial O_2 content (CaO_2), arterial hemoglobin saturation ($HbO_2\%$), and hemoglobin concentration ([Hb]) responses at rest and the five exercise intensities. Values are means (±SE). Data points with the same letter are not significantly different.

increased from a mean (±SD) of 4.0 (±5.6) mm Hg at rest to 22.3 (±6.6) mm Hg at the highest work rate. Individual values at the highest work rate ranged from 11 to 37 mm Hg. The mean ideal PAO_2-PaO_2 difference equaled the mean $PETO_2$-PaO_2 difference at rest (4.1 vs 4.0 mm Hg) but exceeded the mean $PETO_2$-PaO_2 difference during exercise by 4.4–7.0 mm Hg.

None of the athletes possessed a hemoglobin variant with abnormal O_2 binding properties. All of the athletes were classified as hemoglobin Type AA. The mean (± SD) percentages of fetal Hb and HB A_2 were 1.0 (±0.0) and 2.41 (±0.43), respectively, both of which are in the normal range for adults.

Figure 5 depicts the mean $\dot{Q}$ responses at rest and during exercise. Mean (±SD) $\dot{Q}$ rose 3.3-fold from rest (6.1 ± 1.2 $l \cdot min^{-1}$) to the lowest work rate (20.0 ± 2.4 $l \cdot min^{-1}$). At higher work rates, mean $\dot{Q}$ increased significantly and linearly from one exercise intensity to the next. Mean (±SD) $\dot{Q}$ at the highest work rate was 29.4 (±2.7) $l \cdot min^{-1}$. Individual $\dot{Q}$ values at the highest work rate ranged from 26.0 to 37.1 $l \cdot min^{-1}$.

In Figures 6 and 7, the mean DLCO and Dm responses at rest and during exercise are presented. There was a tendency for the DLCOs measured with 21% O_2 to level off with increasing work rate. The mean DLCOs

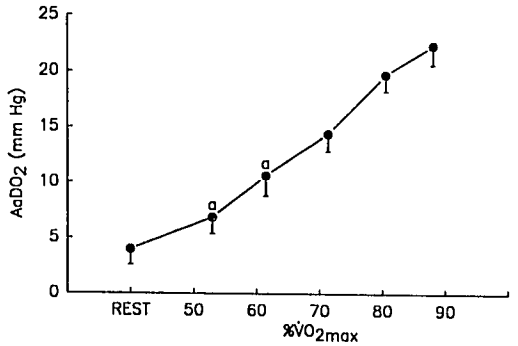

Figure 4—End tidal-arterial O_2 tension difference ($AaDO_2$) responses at rest and the five exercise intensities. Values are means (±SE). Data points with the same letter are not significantly different.

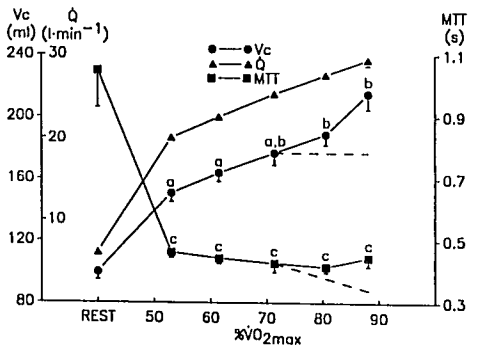

Figure 5—Pulmonary capillary blood volume (Vc), cardiac output ($\dot{Q}$), and mean red blood cell pulmonary capillary transit time (MTT) responses at rest and the five exercise intensities. Values are means (±SE). The *dashed lines* represent the responses of Vc and MTT that would have occurred if Vc had plateaued at a $\dot{Q}$ of 25 $l \cdot min^{-1}$. Data points with the same letter are not significantly different.

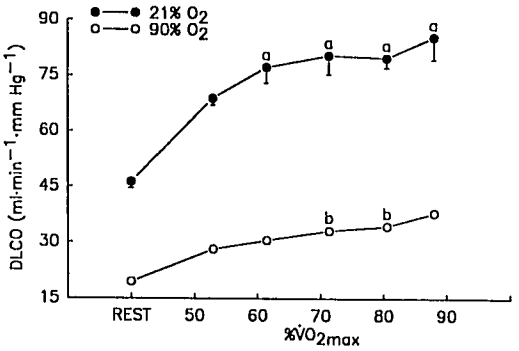

Figure 6—Pulmonary diffusing capacity for carbon monoxide (DLCO) responses at rest and the five exercise intensities. Values are means (±SE). Data points with the same letter are not significantly different.

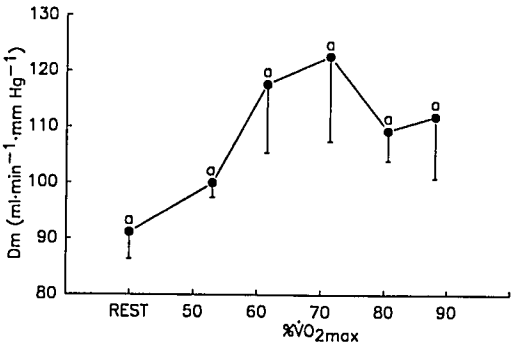

Figure 7—Membrane diffusing capacity (Dm) responses at rest and the five exercise intensities. Values are means (±SE). Data points with the same letter are not significantly different.

from the last four work rates were not significantly different (range, 77.1–85.1 $ml \cdot min^{-1} \cdot mm\ Hg^{-1}$). This trend was not observed for the DLCOs made with 90% O_2. With the exception of the third and fourth work rates, DLCOs (90% O_2) at all work rates were significantly different from each other. Mean Dm did not change with the transition from rest to first work rate or with further increases in exercise intensity (range, 91.2–122.8 $ml \cdot min^{-1} \cdot mm\ Hg^{-1}$).

Mean (±SD) Vc increased by 50% (from 100 (±19.5) to 151 (±20.6) ml) in the transition from rest to the first work rate (Fig. 5). During exercise, Vc increased progressively by an average of 16 ml (SD = 6.7) from one stage to the next and showed no tendency to level off despite the fact mean values over the last three work rates were not significantly different. Vc increased over the last three work rates in 12 of the 16 subjects. At the highest work rate, mean Vc equaled 215 ml (SD = 33.5). At the highest work rate, mean Vc had expanded 2.2-fold over rest compared with a 4.8-fold expansion in mean $\dot{Q}$.

Mean transit time, on average, dropped from 1050 (SD = 476) ms at rest to 463 (SD = 64) ms at the lowest work rate (Fig. 5). Mean transit time, on average, did not decrease further with increasing exercise intensity (range, 417–463 ms). Individual variation in mean

transit time at the highest work rate ranged from 302 to 552 ms.

If exercise-induced hypoxemia resulted from the decline in mean transit time, then the variance in PaO_2 and $AaDO_2$ would be expected to be related to the variance in mean transit time. This was not the case. The variance in mean transit time accounted for only 9.0% ($P = 0.02$) of the variance in the $PETO_2$-PaO_2 difference. Use of ideal PAO_2-PaO_2 difference values did not improve the relation ($R^2 \leq 0.08$). In addition, there was no relation between the individual $AaDO_2$ and mean transit times observed at the highest work rate ($R^2 \leq 0.07$, $P = 0.45$). The relation between the individual PaO_2s and mean transit times observed at the highest work rate was even weaker ($R^2 = 0.06$, $P = 0.83$). Also, there was no critical mean transit time during exercise below which a statistically significant increase in $AaDO_2$ occurred.

DISCUSSION

The objective of this study was to measure $\dot{Q}$, Vc, and mean red blood cell pulmonary capillary transit time during moderate to near-maximal exercise in endurance athletes. The purpose was to test the hypothesis of Dempsey and Fregosi (8) that exercise-induced hypoxemia is caused by a pulmonary diffusion limitation due to a reduction in mean transit time consequent to a plateau in Vc at cardiac outputs above 25 $l \cdot min^{-1}$. The results of this study do not support this hypothesis. During exercise of progressively increasing intensity, in which $\dot{Q}$ exceeded 25 $l \cdot min^{-1}$ and modest hypoxemia developed, Vc increased progressively and mean transit time remained unchanged. Failure of the development of hypoxemia to be accompanied by a plateau in Vc and a reduction in mean transit time could have been because: 1) methodological limitations obscured the relation, 2) marked hypoxemia was not observed in our subjects under the conditions studied, and/or 3) diffusion limitation consequent to a reduction in mean transit time is not the cause of exercise-induced hypoxemia.

Accurate estimation of mean transit time is dependent on accurate measurement of $\dot{Q}$ and Vc. The validity of echocardiography in determining $\dot{Q}$ during exercise is still open to question. Invasive techniques, such as direct Fick and indicator dilution, are generally considered to be superior in accuracy and reliability. However, the reliability and the relation of $\dot{Q}$ to $\dot{V}O_2$ observed for the echocardiographic estimates were almost identical to those of more established methods, suggesting these measures were valid and not a major source of error. Although the DLCO technique for estimation of Vc is considered to be the "gold standard," the technique is hardly noise-free, as evidenced by the test-retest reliability results. This procedure places extreme demands on subject cooperation in the performance of the single-breath DLCO maneuver during heavy exercise. Nevertheless, the reliability of the Vc measures were acceptable, and there is no evidence that there were major systematic errors that would distort the general pattern of the results or obscure the relationships of interest.

Errors in estimation of PaO_2 and $AaDO_2$ could have contributed to the weak relationship found between these variables and mean transit time. Inaccurate arterial blood temperature estimates could have contributed since neither direct nor esophageal temperature measurements were made. Measurement error in estimation of PAO_2 was probably more of a factor. $PETO_2$-predicted and ideal values differed by no less than 4.4 mm Hg during exercise and neither probably equaled the "gold standard" PAO_2, the volume-averaged expired value (1).

Marked hypoxemia during strenuous exercise was observed in only one subject. It is possible that the subjects were not physiologically comparable to those subjects used in studies previously investigating the incidence and/or mechanisms of exercise-induced hypoxemia in endurance athletes (9,21,26,28,35). Yet, the subjects in this study had aerobic capacities comparable to those in the previous studies (mean $\dot{V}O_{2max}$ = 4.90 vs 4.49–4.86 $l \cdot min^{-1}$ and 67.4 vs 64.5–72.1 $ml \cdot kg^{-1} \cdot min^{-1}$). The mean HbO_2% observed at the highest work rate (91.5%) was similar to that reported by Dempsey et al. (9) during maximal treadmill exercise (91.9%) and only slightly higher than the range of pulse oximetric estimates of mean HbO_2% reported during heavy exercise (85.5–90.9%) (21,26,28,35).

The only one of these previous studies to utilize arterial blood gas analysis was that of Dempsey et al. (9). The mean PaO_2 in their study at $\dot{V}O_{2max}$ was 11.7 mm Hg less than that observed in this study at the highest work rate. Eight of their 16 athletes had PaO_2s at $\dot{V}O_{2max}$ of less than 75 mm Hg. In contrast, only one individual in this study had a PaO_2 below 75 mm Hg at the highest work rate. At maximal exercise, Dempsey and coworkers reported a mean ideal PAO_2-PaO_2 difference of 33 mm Hg, some 6 mm Hg greater than observed in this study at the highest work rate. The differences in exercise intensity (100 vs 88% $\dot{V}O_{2max}$) and exercise mode (treadmill vs cycle) may explain the lower PaO_2s and higher $AaDO_2$s in their study.

None of the more recent studies investigating exercise-induced hypoxemia have reported whether CaO_2 falls during heavy exercise. This is important because it has implications for whether these athletes are truly limited by lung function. If exercise-induced hypoxemia has a negative impact on exercise performance, then this should be reflected by a drop in CaO_2 with increasing exercise intensity. We found no drop in CaO_2 with increasing intensity. CaO_2 actually rose 3% from

rest to the highest work rate. The drop in HbO_2% from rest to the highest work rate was offset by a 8% rise in [Hb]. Rowell et al. (31) observed a mean increase (from rest to $\dot{V}O_{2max}$) in CaO_2 of 2% (to 18.2 ml·dl^{-1}) in three of their athletes exhibiting a mean HbO_2% of 85%.

Our results suggest that a reduction in mean transit time was not the primary cause of the increase in $AaDO_2$ and decrease in PaO_2 as exercise intensity progressed from moderate to near-maximal levels. First, mean transit time remained unchanged with increasing work rate and explained no more than 9% of the variance in $AaDO_2$. Second, among the individual athletes, there was no relationship between mean transit time and $AaDO_2$ or PaO_2 at the highest work rate. In other words, the athlete with the shortest mean transit time did not have the largest $AaDO_2$ or the lowest PaO_2. Third, only one athlete was found to have a significant correlation between mean transit time and $AaDO_2$ ($r = 0.88$, $P = 0.02$), but in this individual, PaO_2 rose with increasing work rate.

Yet, a pulmonary diffusion limitation could have contributed to the exercise-induced hypoxemia observed in the athletes in this study. A diffusion limitation has been observed in moderately trained subjects during sea level exercise in which $\dot{V}O_2$ exceeds 2.0–2.5 l·min^{-1} (16). Even though mean transit time failed to decrease with increasing work rate, it is possible that interregional differences in transit time could have resulted in a diffusion limitation and contributed to the $AaDO_2$ widening.

Using a theoretical model, Johnson et al. (17) proposed a Gaussian distribution (SD = 0.1 s) for RBC transit times. Using this distribution, it is predicted that for the mean transit times observed in this study (0.42–0.46 s), 14–24% of the RBC could have had transit times below 0.35 s. To account for the present study's increase in $AaDO_2$ without a concomitant decrease in mean transit time, one would have to predict an increase in the standard deviation of the RBC transit time distribution.

Dempsey (7) has proposed an alternative explanation for the cause of diffusion limitation in endurance athletes. He has hypothesized that the O_2 equilibration rate between alveolar gas and mixed venous blood is slower in highly trained athletes than in lesser-trained individuals. This is suggested to be due to a lower mixed venous O_2 tension ($P\bar{v}O_2$) and PAO_2 in the highly trained athlete during heavy exercise. Theoretically, a reduction in either one of these two partial pressures reduces the O_2 equilibration rate. In the present study, if the O_2 equilibration rate was reduced with increasing work rate, then a diffusion limitation could occur once the required equilibration time dropped below the transit time.

To test this possibility, $P\bar{v}O_2$ was estimated from $C\bar{v}O$ ($= CaO_2 - (VO/Q)$) using the nomograms of Kelman and Nunn (19). This required three assumptions: 1) venous [Hb] was the same as arterial [Hb], 2) venous temperature was the same as sublingual temperature, and 3) venous pH equaled arterial pH minus 0.05. The mean estimated $P\bar{v}O_2$ dropped only slightly from 19.7 mm Hg at the lowest work rate to 16.4 mm Hg at the highest. At the same time, mean $PETO_2$ increased by 11 mm Hg from the lowest to the highest work rate and thus should have acted to offset any reduction in the O_2 equilibration rate brought about by the drop in $P\bar{v}O_2$. This logic is faulted if for equivalent changes in $P\bar{v}O_2$ and PAO_2, the change in $P\bar{v}O_2$ has the greater effect on the O_2 equilibration rate. Otherwise, the data from the present study suggest that the O_2 equilibration rate did not decrease with increasing exercise intensity.

It is also possible that pulmonary interstitial edema or another change in the alveolar-capillary membrane could explain the existence of a diffusion limitation. The only evidence to support this hypothesis is that Dm tended to decline after the third work rate. However, this decline was not statistically significant and the variance in Dm did not explain any of the variation in $AaDO_2$ ($R^2 = 0.0001$, $P = 0.97$). These observations are in agreement with those of Goresky et al. (15) and Marshall et al. (23). They reported that interstitial water accumulation during exercise was minimal and had no adverse effect on gas exchange.

In conclusion, the results of this study do not support the hypothesis that the development of exercise-induced hypoxemia as exercise intensity progresses from moderate to near-maximal levels results from a decrease in mean transit time. In highly trained endurance athletes, Vc continues to increase with $\dot{V}O_2$ and $\dot{Q}$ above 3.5 and 25 l·min^{-1}, respectively, and because of this, mean transit time is maintained in the 0.4–0.5 s range. The findings do not rule out the possibility that a diffusion limitation may be the cause of the exercise-induced hypoxemia in athletes, however.

The authors express gratitude for the hemoglobin analyses performed by Drs. Titus H. J. Huisman and Abdullah Kutlar of the Department of Cell and Molecular Biology, School of Medicine, Medical College of Georgia, Augusta, GA 30912.

This study was supported in part by services and equipment made available by St. Mary's Hospital, Athens, GA, and by P. K. Morgan Instruments, Inc.

Address for correspondence: Gordon L. Warren, Exercise Biochemistry Laboratory, Physical Education Building, The University of Georgia, Athens, GA 30602.

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