Alveolar epithelial integrity in athletes with exercise-induced hypoxemia

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The effect of incremental exercise to exhaustion on the change in pulmonary clearance rate (k) of aerosolized 99mTc-labeled diethylenetriaminepentaacetic acid (99mTc-DTPA) and the relationship between k and arterial Po2 (PaO2) during heavy work were investigated. Ten male cyclists (age = 25 ± 2 yr, height = 180.9 ± 4.0 cm, mass = 80.1 ± 9.5 kg, maximal O2 uptake = 5.25 ± 0.35 l/min, mean ± SD) completed a pulmonary clearance test shortly (39 ± 8 min) after a maximal O2 uptake test. Resting pulmonary clearance was completed ≥24 h before or after the exercise test. Arterial blood was sampled at rest and at 1-min intervals during exercise. Minimum PaO2 values and maximum alveolar-arterial Po2 difference ranged from 73 to 92 Torr and from 30 to 55 Torr, respectively. No significant difference between resting k and postexercise k for the total lung (0.55 ± 0.20 vs. 0.57 ± 0.17 %/min, P > 0.05) was observed. Pearson product-moment correlation indicated no significant linear relationship between change in k for the total lung and minimum PaO2 (r = −0.26, P > 0.05). These results indicate that, averaged over subjects, pulmonary clearance of 99mTc-DTPA after incremental maximal exercise to exhaustion in highly trained male cyclists is unchanged, although the sampling time may have eliminated a transient effect. Lack of a linear relationship between k and minimum PaO2 during exercise suggests that exercise-induced hypoxemia occurs despite maintenance of alveolar epithelial integrity.

Pulmonary clearance of technetium-99m-diethylenetriaminepentaacetic acid; alveolar epithelium; gas exchange

EXERCISE-INDUCED HYPOXEMIA (EIH), defined as the inability to maintain arterial Po2 (PaO2) and arterial oxyhemoglobin saturation (SaO2) during exercise, occurs in some high-aerobic-power athletes and is associated with a widened alveolar-arterial Po2 gradient (A-aPo2) (3, 4, 12, 29). The precise etiology of EIH and the widened A-aPo2 remains unclear but is likely the result of, or an interaction among, relative alveolar hypoventilation, ventilation-perfusion (V˙A/Q˙) inequality, and diffusion limitations (3, 25). Hopkins et al. (12), using the multiple inert gas elimination technique, reported that 60% of the widened A-aPo2 in highly trained athletes could be explained by V˙A/Q˙ inequality, whereas the remainder was attributed to a diffusion limitation. This group has also reported that athletes who develop EIH have high cardiac outputs, low mixed venous Po2, and shortened pulmonary transit times (10).

Several authors have suggested that intense exercise might result in injury to the alveolar-capillary membrane. West et al. (34) introduced the concept of “stress failure” after they demonstrated disruptions to the capillary endothelium, alveolar epithelium, and their respective basement membranes, in a rabbit lung model when pulmonary arterial pressures were raised to ≥40 Torr. Indirect evidence that may support the theory of stress failure in humans includes several anecdotal reports of human athletes who have coughed up or tasted blood after strenuous exercise (32, 33). In addition, an increase in red blood cells (RBCs) and protein has been reported in bronchoalveolar lavage fluid obtained after 7 min of maximal exercise (13). This finding supports the theory that structural failure of the blood-gas barrier can result from heavy physical work. However, in these studies, PaO2 or SaO2 was not measured, which leaves the relationship between blood-gas barrier integrity and gas exchange during intense exercise unresolved.

High pulmonary capillary perfusion pressure during heavy exercise may result in damage to the pulmonary capillaries and altered integrity of the blood-gas barrier. To permit efficient gas exchange by diffusion, the barrier between the alveoli and the capillaries must be extremely thin. In some sections it may measure only 0.3 μm (7). In contrast, the blood-gas barrier must also be strong enough to withstand elevated pulmonary vascular pressure associated with high cardiac output during intense exercise.

99mTc-labeled diethylenetriaminepentaacetic acid (99mTc-DTPA) has been used as a nonspecific, but ex-
HEAVY EXERCISE AND PULMONARY DTPA CLEARANCE

extremely sensitive, method for detecting lung pathology (1, 22). \(^{99m}\text{Tc-DTPA} \text{ is hydrophilic and normally limited to passive diffusion through the intercellular junctions of the alveolar epithelium and the capillary endothelium (5, 15). Alveolar epithelial junctions are 10 times less permeable than capillary endothelial junctions (8), and therefore diffusion of \(^{99m}\text{Tc-DTPA} \text{ through the blood-gas barrier is primarily dependent on the permeability of the alveolar epithelial membrane. Damage to the blood-gas barrier during exercise, sufficient to alter permeability of the alveolar epithelium, would likely be detected by the change in the pulmonary clearance rate of \(^{99m}\text{Tc-DTPA}. We hypothesized that alveolar epithelial permeability in highly trained cyclists after an incremental exercise test to exhaustion would be increased and related to the impairment in gas exchange.

METHODS

Subjects and preliminary tests. Subjects reported to the laboratory ≥3 h postprandial and 24 h after exhaustive exercise. Spirometry involved resting measurements of forced vital capacity, forced expiratory volume in 1 s, and maximal forced expiratory flow (MedGraphics CPX-D Metabolic Cart, St. Paul, MN). A maximal \(\text{O}_2 \) uptake (\(\text{VO}_2\text{max} \)) test was performed on an electronically braked cycle ergometer (Quinton Excalibur, Gronigen, The Netherlands) starting at 0 W and increasing by 30 W/min until volitional fatigue. A minimum \(\text{VO}_2\text{max} \) of 65 ml·kg\(^{-1}\)·min\(^{-1}\) or 5.0 l/min [determined as the average of the 2 highest consecutive 15-s \(\text{O}_2 \) consumption (\(\text{VO}_2 \)) scores] was required for further participation in the study. Ten competitive male cyclists or triathletes who met this criterion were selected. All subjects were nonsmokers and had no history of cardiorespiratory disease. Participants signed an informed consent that described the inherent risks associated with the study. All experimental procedures were approved by the University Clinical Ethics Review Board.

Experimental protocol. At least 48 h after preliminary tests, subjects returned to the laboratory. On arrival, an arterial catheter was inserted into the radial artery of the nondominant wrist before exercise, and blood was sampled to measure \(\text{PaO}_2\), \(\text{PCO}_2\) (\(\text{PaCO}_2\)), bicarbonate (\(\text{HCO}_3\)), and pH. After catheter insertion, subjects completed a \(\text{VO}_2\text{max} \) test (with use of the same protocol described in the preliminary tests). Arterial blood samples (3 ml) were collected immediately before the onset of exercise and at 1-min intervals (starting at minute 4) for the duration of the exercise test. Minute ventilation, \(\text{VO}_2\), and heart rate (HR) were continuously measured during exercise. Pulmonary clearance was determined using \(^{99m}\text{Tc-DTPA} \text{ aerosol in all subjects shortly after the exercise test, with an average time interval between the completion of the exercise test and after pulmonary clearance of 38 ± 8 (SD) min. Resting pulmonary clearance was completed ≥24 h before or after the exercise test. HR was recorded during both lung clearance tests.

Instrumentation. Ventilatory parameters were measured for the duration of the exercise tests with a low-resistance, two-way nonbreathing valve (model 2700B, Hans Rudolph) and a 5-liter mixing chamber for collection of expired gases. From this chamber, continuous samples of air were analyzed for concentrations of \(\text{O}_2 \) and \(\text{CO}_2 \) at a rate of 300 ml/min (S-3A \(\text{O}_2 \) analyzer and CD-3A \(\text{CO}_2 \) analyzer, Applied Electrochemistry). Analyzers were calibrated with gases of known concentration before each test. Inspired ventilation was measured with a flowmeter (model 17150, Vacumetrics). This device was calibrated by pumping 100 liters of air through the system. Average ventilatory and gas exchange parameters were recorded every 15 s with use of a computerized system (Rayfield, Waitsfield, VT). HR was measured continuously and recorded every 15 s with a portable HR monitor (Polar Vantage XL, Kempele, Finland).

Following Allen’s test for collateral circulation, a 20-gauge arterial catheter was inserted into the radial artery of the nondominant wrist by percutaneous cannulation with 1% lidocaine and sterile technique. Minimum-volume extension tubing, connected in series with two three-way stopcocks arranged at right angles, was flushed with saline-heparin solution (1 ml of 1:1,000 U in 500 ml of normal saline). A rapid-response (<0.1 s) thermistor (model 187T, Physistemp Instruments, Clifton, NJ) was inserted through a Touhy-Borsch heparin lock (Abbott Hospitals, North Chicago, IL) and used to measure peak arterial blood temperature during collection of the blood sample. Catheter patency was maintained with intermittent heparin infusion (<3 ml/h). Blood samples were placed on ice until analyzed for \(\text{H}^+ \) concentration, \(\text{PO}_2\), \(\text{PaCO}_2\), and \(\text{HCO}_3\) (model 278 blood-gas system, CIBA-Corning Diagnostics, Medfield, MA). Blood gases were corrected for temperature. Arterial blood temperature increased 0.8 ± 0.2°C during the \(\text{VO}_2\text{max} \) test. \(\text{SaO}_2 \) levels were calculated on the basis of \(\text{PaO}_2 \), changes in body temperature, and pH. The alveolar gas equation was used to calculate the alveolar \(\text{PO}_2 \) and A-a\(\text{PO}_2 \) (23).

The aerosol was created in a nebulizer by introducing 20–30 mCi (740–1,110 MBq) of \(^{99m}\text{Tc-DTPA} \text{ in 2 ml of saline and driving it with compressed air at a flow rate of 10 l/min (Venti-Scan III Disposable, Biodex Medical, New York, NY). Breathing procedures were rehearsed before inhalation of the aerosol to ensure optimal delivery. Each subject was fitted with a noseclip and a mouthpiece and instructed to breathe through a two-way valve at normal tidal volumes for 3 min in the seated position. The exhalate was trapped in a filter. A dose of ~1–2 mCi (37–74 MBq) was administered to the subject. The subject was seated with a large field-of-view gamma scintillation camera (Siemens Orbiter, Iselin, NJ) positioned posteriorly and set to image the entire lungs for 30 min. Subjects were instructed to remain motionless during data acquisition.

Data analysis. Output from the gamma camera was processed by computer. Decline in radioactivity over time was recorded in 30-s image frames consisting of a computer image of 128 × 128 pixels. Computer analysis of regions of interest was carried out around each lung (left and right); then each lung was further divided into regions corresponding to apical and basal regions. The data obtained for the total, left, right, apical, and basal regions were corrected for physical decay and then plotted as a function of time. The data for all regions were fit by a monoexponential function: \(N = N_0 e^{-kt} \), where \(N_0 \) is the y-intercept or count rate at time 0, \(N \) is the count rate at any time \(t \) (min), and \(k \) is the rate constant for clearance. Total (\(k_T \)), right (\(k_R \)), left (\(k_L \)), apical (\(k_A \)), and basal (\(k_B \)) clearance rate constants were determined over the acquisition period and expressed as a percentage of decreased radioactivity per minute (%/min). No correction for recirculation was made.

Statistical analyses. Differences in resting \(k_T \) and postexercise \(k_T \) were analyzed by one-way ANOVA with repeated measures. Two (resting/postexercise) × 2 (region) ANOVAs with repeated measures on both factors were used to assess differences for \(k_B \) and \(k_A \), as well as differences for \(k_R \) and \(k_L \). Pearson product-moment correlation was used to determine...
the strength of the linear relationship between PaO2 and A-aPO2 and between the change in kT (ΔkT = postexercise kT - resting kT) and the minimum PaO2, measured during exercise. A t-test for dependent means was used to determine differences between HRs measured during the pulmonary clearance tests. A t-test for dependent means was also used to determine differences between PaO2 measured before exercise and at maximum exercise. All significance was set at α < 0.05.

RESULTS

Performance. Anthropometric and lung parameters are shown in Table 1. Forced vital capacity, forced expiratory volume in 1 s, and maximal forced expiratory flow were within normal values predicted for men of similar age, height, and weight. Performance variables obtained at maximal exercise are shown in Table 2. Maximum respiratory exchange ratio exceeded 1.15 and peak HR exceeded 90% of maximum predicted HR (220 - age) in all subjects.

Gas exchange. Figure 1 shows individual PaO2, A-aPo2, and PaCO2, respectively, during the progressive exercise test. Mean PaO2 at maximal exercise decreased significantly from resting levels (from 114.3 ± 4.4 to 87.1 ± 8.4 Torr, P < 0.05). In three subjects the lowest PaO2 during exercise remained between 90 and 100 Torr, in five subjects the lowest PaO2 fell to 80–90 Torr, and in the three remaining subjects PaO2 during exercise fell to <80 Torr. The maximum A-aPo2 ranged from 30 to 55 Torr [42.5 ± 7.0 (SD) Torr]. There was a significant negative correlation between PaO2 and A-aPo2 (r = −0.94, P < 0.05). At maximal exercise, five subjects decreased PaCO2 levels below 36 Torr, whereas in four subjects, PaCO2 values did not fall below 38 Torr. Arterial pH and HCO3 levels remained unchanged from light to moderate exercise intensity but progressively declined during moderate to heavy exercise. Minimal values at maximal exercise for pH and HCO3 reached 7.2 ± 0.1 and 14.1 ± 2.5 mmol/l, respectively.

Pulmonary clearance. The quality of the goodness of fit (R2) for the total lung averaged 0.99. The resting and postexercise kT for individual subjects is shown in Fig. 2. Pulmonary clearance rates averaged over subjects for each region at rest and after exercise are shown in Fig. 3.

One-way ANOVA demonstrated that resting and postexercise kT values averaged over subjects were not significantly different (0.55 ± 0.20 and 0.57 ± 0.17%/min, respectively, F = 0.10, P > 0.05).

Table 1. Physical characteristics and spirometry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value ± SD</th>
</tr>
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<tbody>
<tr>
<td>Age, yr</td>
<td>25 ± 2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>180.9 ± 4.0</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>80.1 ± 9.5</td>
</tr>
<tr>
<td>FVC, liters</td>
<td>5.9 ± 0.7</td>
</tr>
<tr>
<td>FEV1, liters</td>
<td>4.9 ± 0.5</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>82.9 ± 5.7</td>
</tr>
<tr>
<td>MFEF, l/s</td>
<td>10.7 ± 1.2</td>
</tr>
</tbody>
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Values are means ± SD; n = 10. FVC, forced vital capacity; FEV1,FVC, forced expiratory volume in 1 s; MFEF, maximum forced expiratory flow.

Table 2. Performance and ventilatory parameters at maximum exercise

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>186 ± 11</td>
</tr>
<tr>
<td>VE, l/min</td>
<td>201.5 ± 22.0</td>
</tr>
<tr>
<td>Power, W</td>
<td>478 ± 31</td>
</tr>
<tr>
<td>VO2max, l/min</td>
<td>5.25 ± 0.35</td>
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<tr>
<td>VO2max, ml·kg⁻¹·min⁻¹</td>
<td>66.1 ± 6.6</td>
</tr>
<tr>
<td>VCO2, l/min</td>
<td>6.46 ± 0.38</td>
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<tr>
<td>RER</td>
<td>1.23 ± 0.06</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 10. HR, heart rate; VE, minute ventilation; VO2max, maximum O2 consumption; VCO2, maximum CO2 production; RER, respiratory exchange ratio.

The region main effect for kL and kR was not significant (F1,9 = 1.13, P > 0.05), indicating that, averaged over rest and after exercise, there were no differences in clearance rates between the right (0.58 ± 0.21%/min) and left lungs (0.54 ± 0.22%/min). The time main effect for rest and after exercise was not significant (F1,9 = 0.09, P > 0.05), indicating that, averaged over left and right lung regions, there were no differences in clearance rates between rest and postexercise (0.55 ± 0.21 and 0.57 ± 0.20%/min, respectively). The region × time interaction was also not significant (F1,9 = 2.25, P > 0.05), indicating that differences in kL and kR had similar clearance rates at rest and after exercise.

The region main effect for kA and kB was significant (F1,9 = 13.9, P < 0.05), indicating that, averaged over rest and after exercise, there were differences in clearance rates between the apical and basal regions (0.83 ± 0.34 and 0.38 ± 0.25%/min, respectively). The time main effect for rest and postexercise was not significant (F1,9 = 0.43, P > 0.05), indicating that, averaged over apical and basal lung regions, there were no differences in clearance rates between rest and postexercise (0.60 ± 0.38 and 0.61 ± 0.37%/min, respectively). The region × time interaction was not significant (F1,9 = 0.23, P > 0.05), indicating that differences in kA and kB had similar clearance rates at rest and after exercise.

HRs determined during the inhalation of the aerosol were significantly greater after exercise than at rest (74 ± 12 vs. 57 ± 8 beats/min, t = 5.4, P < 0.05).

Pulmonary clearance and gas exchange. There was no significant relationship (r = −0.26, P > 0.05) between the minimum PaO2 obtained during the exercise test and ΔkT (Fig. 4). In addition, there was no significant relationship (r = 0.07, P > 0.05) between the maximal A-aPo2 and ΔkT.

DISCUSSION

Pulmonary clearance and exercise. The VO2max values and peak power outputs indicated that these subjects were highly trained, whereas the range of EIH and A-aPo2 during exercise were consistent with other studies involving highly trained male athletes (3, 12, 24).

The present study failed to demonstrate a change in alveolar epithelial permeability in humans after incremental exercise to exhaustion. In addition, no relation-
ship between minimum $P_{aO_2}$ during exercise and change in pulmonary clearance rate was observed, suggesting that exercise-induced hypoxemia and an elevated $A-aP_{O_2}$ occur in these subjects, despite maintenance of alveolar epithelial integrity.

The mechanism(s) of exercise-induced elevation of $A-aP_{O_2}$ and reduction of $P_{aO_2}$ remains unclear. Schaf-fartzik et al. (25) suggested that a transient pulmonary interstitial edema could explain the $V_{A}/Q_{A}$ inequality observed during exercise and in the immediate recovery period. Human pulmonary arterial pressures at maximal exercise can reach 40 mmHg (31), which is in the range shown to cause stress failure of the blood-gas barrier in a rabbit lung model (34). At this magnitude, raised transmural pulmonary vascular pressures in rabbits show disruption to the capillary endothelium and the alveolar epithelium, and in some cases RBCs can be seen passing through the membranes (30, 34). RBCs and protein have been recovered from bronchoalveolar lavage fluid from athletes after 7 min of heavy exercise compared with resting sedentary controls (13). These results suggested loss of blood-gas barrier integrity. All six athletes recruited, however, had a history of hemoptysis after intense exercise. None of the athletes in the present study had such a history. Therefore, the conclusions from this study and the present one may not be comparable.

Hopkins et al. (14) performed broncholavage in athletes after 1 h of submaximal exercise (77% of $V_{O_2 \text{ max}}$) and found no evidence of RBC and protein, indicating no or little damage to the membrane. There was an unexpected finding of RBCs in the lavage fluid of resting control subjects, questioning the sensitivity of this technique for investigating blood-gas barrier integrity.

![Fig. 1. Individual time course data for arterial $P_{O_2}$ ($P_{aO_2}$), alveolar-arterial $P_{O_2}$ gradient ($A-aP_{O_2}$), and arterial $P_{CO_2}$ ($P_{aCO_2}$) during the progressive exercise test. Dashed line, line of identity.](image1)

![Fig. 2. Individual pulmonary clearance rates for the total lung ($k_T$) at rest and after exercise.](image2)

![Fig. 3. Mean values ($n = 10$) for pulmonary clearance rates ($k$) at rest and after exercise and divided into basal ($k_B$), apical ($k_A$), right ($k_R$), and left ($k_L$) regions as well as total lung ($k_T$). Error bars, SD. *Significantly different ($P < 0.05$) from basal region.](image3)
Collectively, it appears that prolonged submaximal exercise may alter Starling’s forces and result in a net fluid flux with or without alteration of the structural integrity of the blood-gas barrier. Unfortunately, none of these studies measured PaO₂ or SaO₂, and, therefore, it is unknown whether extravascular lung water from submaximal exercise is of sufficient magnitude to impair gas exchange.

The results from the present study do not exclude pulmonary interstitial edema as a possible mechanism for the EIH and elevated A-aPO₂ observed in our subjects, inasmuch as this method is not a sensitive indicator of hemodynamically induced pulmonary edema. Indeed, patients with cardiogenic edema can have a normal DTPA clearance, despite significant clinical edema (18).

Lorino et al. (16) assessed pulmonary clearance with ⁹⁹ᵐTc-DTPA in seven healthy volunteers before and after 75 min of exercise corresponding to 75% of the subject’s VO₂ max. After exercise, total, apical, and basal clearance rates were significantly increased. They concluded that the increased alveolar permeability was related to the mechanical effects of prolonged, high ventilation rates. This is compatible with data from the rabbit model where increasing lung volumes along with constant pulmonary arterial pressure increased the incidence of stress failure in rabbits (6). In a pilot study we investigated whether ventilation rates alone would alter alveolar permeability in five subjects. Isocapnic ventilation rates were assigned following data previously obtained during a VO₂ max test (~15 min duration). Mean minute ventilation reached a maximum value of 145 ± 29 l/min during isocapnic ventilation. Total pulmonary clearance rates remained unchanged before and after (30 ± 5 min) the VO₂ max test (0.54 ± 0.02 and 0.57 ± 0.03%/min, respectively, P > 0.05).

VO₂ max values in the study by Lorino et al. (16) only reached 53 ± 3 ml·kg⁻¹·min⁻¹, and the VO₂ during the 75 min of exercise was 40 ± 2 ml·kg⁻¹·min⁻¹. We believe that stress failure would have been unlikely in these subjects, inasmuch as pulmonary arterial pressures do not reach high values during submaximal exercise, even if exercise is prolonged (11). Therefore, it seems unlikely that mechanical effects of sustained ventilation and/or stress failure altered the alveolar epithelial permeability in the study by Lorino et al. Their exercise period was much longer than that in the present study (75 vs. 16 min), and the DTPA measurement was made 25 min after exercise vs. 40 min after exercise in this study. It is possible that the differences in pulmonary clearance rate are a result of the longer exercise duration, or possibly the longer recovery period in the present study missed a transient change in pulmonary clearance immediately after exercise. For many reasons, the study by Lorino et al. is not comparable to the present investigation.

St. Croix et al. (27) have argued that EIH during heavy exercise may reflect a functionally based mechanism, present only during exercise, rather than stress failure; a structural mechanism would be expected to have lasting effects. Their subjects performed a progressive incremental exercise test to VO₂ max followed by a constant load at maximal workload 20 min later. A slight improvement in PaO₂ and A-aPO₂ was found during the second exercise bout. Therefore, a functional mechanism, such as decreased mixed venous O₂ saturation, combined with high cardiac output to an already fully dilated and recruited pulmonary vasculature, may decrease pulmonary capillary transit time and result in decreased end-capillary O₂, widened A-aPO₂, and EIH (10).

Methodological concerns. All subjects in the present study were nonsmokers. Pulmonary clearance rates in our subjects at rest were considered normal for healthy individuals (26). Faster apical than basal clearance rates reflect greater apical ventilation and greater surface area available for diffusion of ⁹⁹ᵐTc-DTPA (17, 18, 21).

It is possible that blood-gas barrier remodeling occurred in the time delay between the exercise test and the postexercise pulmonary clearance test. This time delay was designed to allow pulmonary blood flow and ventilation to return to near resting values. However, HRs recorded during the inhalation of the aerosol remained significantly elevated after exercise compared with resting, and it is uncertain whether pulmonary capillary blood volume and/or the area available for gas exchange was altered.

Background correction for recirculation of radioactivity through the pulmonary capillaries is a contentious issue (2). Several studies (16, 20) have ignored recirculation and have argued that background radioactivity does not significantly affect the measured clearance rate. It is known that the rate at which the aerosol leaves the blood by normal kidney filtration is 10-fold faster than the rate the aerosol enters the blood through the blood-gas barrier (9). In contrast, using the liver for background correction, Mason et al. (19) recently demonstrated that when intravenous DTPA was administered before inhalation of the aerosol, pulmonary clearance curves were multieponential. However, when the thigh was used for background correction, the pulmonary clearance curves were mono-
exponential. Apparently, the liver has a closer extravascular-to-intravascular compartment ratio to the lung, and therefore the authors concluded that liver background correction allows the true shape of the curve to be identified. Clearance curves in the present study were analyzed for 30 min and not corrected for recirculation. Staub et al. (28) reported that correction for recirculation was less of a concern if clearance curves were calculated within this time period.

In conclusion, averaged over subjects, pulmonary clearance of $^{99m}$Tc-DTPA after incremental maximal exercise to exhaustion in highly trained male cyclists was unchanged. Furthermore, there was no relationship between altered pulmonary clearance and the minimum $P_{aO_2}$ during heavy exercise, suggesting that exercise-induced hypoxemia occurs despite maintenance of alveolar epithelial integrity.

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