Exercise Increases the Lung Clearance of Inhaled Technetium-99m DTPA

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The regional lung clearance of a deposited aerosol of [^{99m}Tc] diethylenetriaminepentaacetic acid was successively computed at rest and at exercise in seven nonsmoking volunteers in upright posture. The subjects were seated on a bicycle with their backs against a gamma camera. At rest there was a gradient of clearance from the apex to the base of the lung, the apical clearance being significantly higher. At exercise this regional gradient was enhanced by a large and significant increase of the apical clearances (3.40 ± 0.63% min^{-1} s.d. compared with 1.82 ± 0.75% min^{-1} s.d. at rest, $n = 7$, $p < 0.01$). By contrast the changes of the basal clearances were slight and unsignificant (1.46 ± 0.71% min^{-1} s.d. compared with 1.40 ± 0.82% min^{-1} s.d.). This increase of the apical lung clearance could be attributed primarily to the increase of apical blood flow induced by exercise and to the subsequent increase of the permeability surface area product.

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In recent studies, the measurement of the lung clearance of aerosolized technetium-99m diethylenetriaminepentaacetic acid ([^{99m}Tc]DTPA) has been used to assess the alveolobronchiolar permeability in both smoking and nonsmoking normal subjects and in patients (*1–5*). Technetium-99m DTPA is a small hydrophilic molecule (molecular weight 492 daltons) rapidly cleared by the lungs and, supposedly, crossing the alveolar capillary barrier through interepithelial junctions (*6*). However, little is known about the variations of this clearance with regards to pharmacologic or physiologic conditions which lead to changes of the distribution, perfusion, or ventilation within the lung (*7*). Exercise is known to induce drastic changes of regional ventilation and perfusion of the lung which have been thoroughly studied (*8, 9*). Therefore, we studied the effect of a mild exercise performed in seated posture on the regional lung clearance of [^{99m}Tc]DTPA in order to better understand the mechanism involved in the transport of this molecule.

MATERIALS AND METHODS

Experimental Group

Seven healthy nonsmoking volunteers, three men and four women, age ranging from 25 to 36 yr, were selected for the experimental procedure. An aerosol of droplets was generated from a 30 mCi (1.11 × 10^9Bq) [^{99m}Tc]DTPA solution in 10 ml 9% sodium chloride using a glass nebulizer under 1.5 bar pressure and at a flow rate of 25.1 min^{-1}. The droplets were then dried by flowing through a fenestrated pipe surrounded by silicagel. The air stream containing the dry residue continuously flowed through a broad-bore tube where the subject inhaled this dry aerosol through the inspiratory valve of a face mask. The radioactivity from the tube and from the expiratory line was removed by means of a low-resistance filter. The characteristics of the dry particles were measured with an electrical mobility analyzer[†] as described (*10*). The particles had a count median diameter of 0.045 μ, a geometric deviation of 1.7 resulting in a mass median diameter of 0.6 μ.

The subjects were submitted to the following procedure. They breathed the aerosol with a normal tidal volume for 5 min. The expiratory gases were collected from the expiratory line during the inhalation. The subjects then sat on an ergometric bicycle, their backs in front of a large field gamma-camera[‡] linked to a minicomputer[§]. A surgical strip placed under their shoulders prevented the subjects from moving. The lung field radioactivity data were framed at 1 min intervals during a resting and an exercising period; resting period

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lasted 20 min. As the twentieth frame was achieved, the exercise period started. Exercise was sustained for the next 7 min at 50 W with a pedal speed of 60-70 cycles $\min^{-1}$. The subjects had previously kept their shoulders carefully against the camera during pedaling for another experimental procedure. The respiratory and heart rate were recorded immediately prior to and at the completion of exercise.

One region of interest (ROI) was selected over each lung, on the first image of the resting phase, and subsequently divided at the level of the hilum by a horizontal line resulting in two other ROIs corresponding to upper and lower lung fields (later referred to as apex and base). These ROIs were applied to all the framed data of each study. Radioactivity was corrected for radionuclide decay and the data were submitted to a monoexponential regression analysis. An exponential line of best fit was calculated for each ROI. The negative slope of this regression line was designated as the clearance rate "k" and was expressed in terms of percentage decrease of the radioactivity per min (% $\min^{-1}$). The clearance rates of the right and left total lung fields, apices, and bases were computed on the data obtained during the 20-min resting period. In order to make an adequate comparison with the data obtained during the 7-min exercising period, the clearance rates were also computed on the first 7 min of the resting period. However, to compute the clearance rates of apices and bases on these 7-min intervals, the count rates from both apices or both bases were added for statistical reasons. Using this process, at the beginning of the resting period the initial count rate over the apical ROIs averaged 14,143 ± 6,567 per min. The regression lines obtained corresponded closely at rest and at exercise to the data point: The correlation coefficients (r) were always > 0.95 for the 20-min clearances and always >0.90 for the 7-min clearances. No correction was done for radioactivity contained in pulmonary blood pool, or chest wall.

To check the possibility that the DTPA clearance during the exercise could be influenced by the mucociliary transport, two roughly rectangular ROI chosen to represent 10% of the area of each lung image and centered around the hilus were drawn. The integrated count rates did not increase in these ROIs between the first and the seventh minute of the exercising period. In contrast, a slight decrease was observed in both regions (1,525 ± 650 cpm compared with 1,380 ± 820 for the right lung, $n = 7$, N.S., 1,344 ± 748 cpm compared with 880 ± 455 cpm for the left lung, $n = 7$, $p <0.02$).

To assess the influence of the extrapulmonary thoracic background (stomach, renal, hepatosplenic activity) on the measurements of lower lung field activity, the count rate value in a rectangular ROI drawn between the lung bases and the kidneys was computed. This value did not change significantly with time (768 ± 412 cpm in the first minute compared with 965 ± 552 cpm in the twenty-seventh min). The mean count per pixel averaged 16.8 ± 2.4% of the mean count pixel obtained in the basal ROI of the lung.

Control Studies

In three subjects (1, 5, 7) the regional ventilation per unit volume was measured at rest and after 7 min of exercise at 50W using the washout curves of inhaled krypton-81m (^{81m}Kr). For each experimental condition, minute ventilation was measured with a classic spirometer and a posterior view of 300,000 counts was recorded during steady state inhalation of the gas delivered through a face mask. Inhalation was then discontinued by removal of the mask. One-second frames were recorded during the washout phase. Radioactivity curves were obtained from the apices and the bases of the lungs. A line was fitted to the initial uncorrected exponential section of the washout curve to give the clearance (including both physical decay and biological clearance). Ventilation per unit alveolar volume ($\dot{V}/V$) was then calculated by substracting the decay constant of ^{81m}Kr (3.2 $\min^{-1}$) as previously described (*11*). The apicobasal ratios of ventilation per unit volume were expressed at rest and at exercise.

In order to test the influence of the duration of the acquisition on the [^{99m}Tc]DTPA clearance values, a control study was performed in five other nonsmoking subjects ranging in age from 27 to 40 yr. After the inhalation, the lung radioactivity was followed during 27 min, at rest. The clearance rates were computed as previously described during the first 7 min and between the twentieth to the twenty-seventh minutes of the study.

Statistical Methods

Comparisons among the clearances of the total lung field at rest and at exercise were performed using a two-factor analysis of variance within each group. Comparisons among the clearances of apices and bases at rest and at exercise were performed between the experimental and the control group using a three-factor variance analysis with repeated measurements (*12*) followed by a two-factor analysis. Student's paired t-test was used for other comparisons. Values were expressed as the mean ± s.d., p value 0.05 was accepted as indicating statistic significance.

RESULTS

Rest

In the seven subjects the mean tidal volume during inhalation was 460 ml ± 259 and the deposition of the aerosol was homogeneous (Fig. 1). Their mean respiratory rate before exercise was 12.7 ± 3 $\min^{-1}$. Their mean heart rate was 94 ± 10 $\min^{-1}$ which can be explained by some initial anxiety before starting to pedal (Table 1). The clearance rates of their total lung field measured at rest were not significantly different whether computed in the first 7 min (Table 2) or during the 20 min of the resting period: 1.56 ± 1.11% $\min^{-1}$ for the right lung and 1.46 ± 0.55% $\min^{-1}$ for the left lung compared with 1.45 ± 0.87% $\min^{-1}$ and 1.23 ± 0.58% $\min^{-1}$, respectively.

The clearance rates computed during the entire resting period in each apex and base showed that the apical clearances were significantly higher than the basal clearances 1.88 ± 0.95% $\min^{-1}$ compared with 1.30 ± 0.76% $\min^{-1}$ ($p <0.05$, $n = 7$) for the right lung and 1.59 ± 0.58% $\min^{-1}$ compared with 1.11 ± 0.55% $\min^{-1}$ ($p <0.02$, $n = 7$) for the left lung (Fig. 2). No difference was found between the right and left lung by the variance analysis.

At rest, the apical $\dot{V}/V$ computed with ^{81m}Kr was lower than the basal V/V (0.7 ± 0.2 $\min^{-1}$ compared with 1.26 ± 0.2 $\min^{-1}$). The distribution of $\dot{V}/V$ between the apex and base was 1: 1.6.

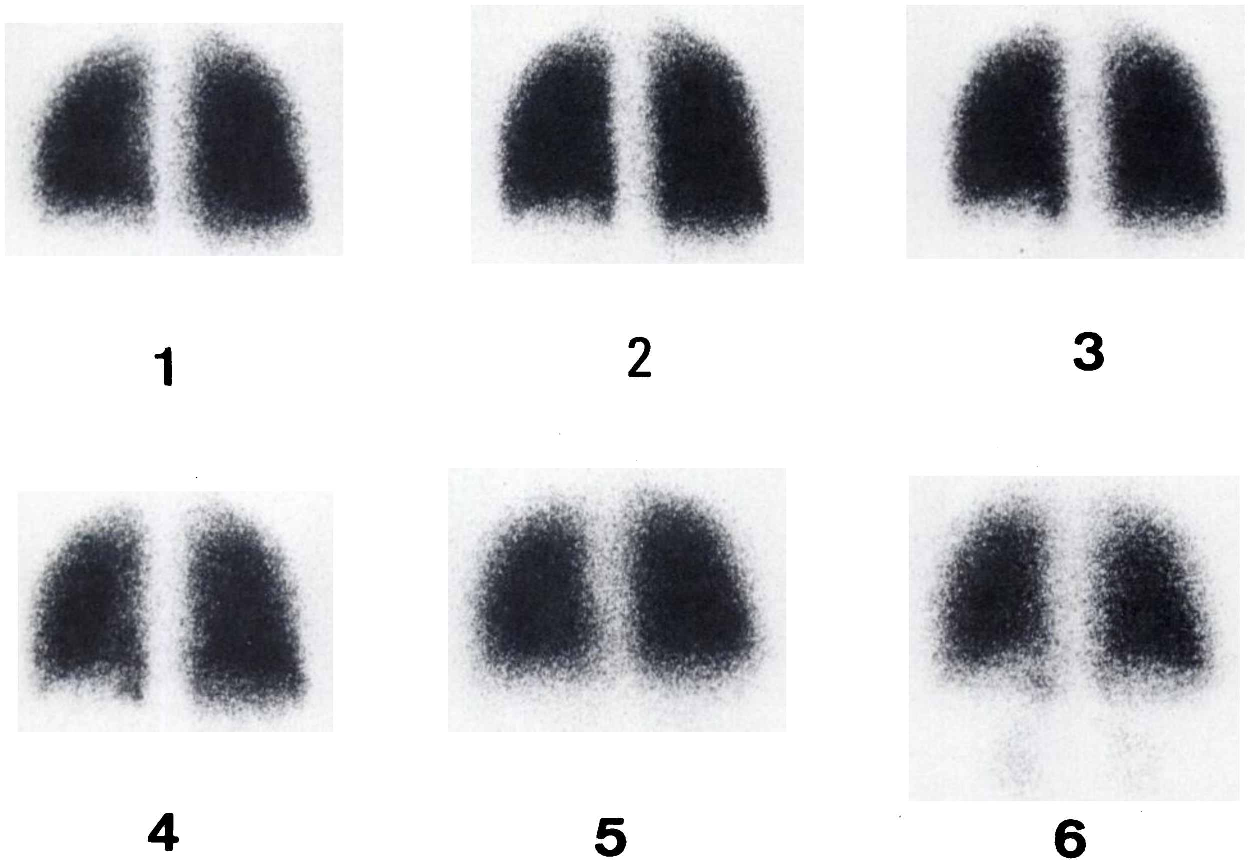

FIGURE 1
Scan for [^{99m}Tc]DTPA in subject 6. Six scintigraphic images in posterior views are shown, obtained every 5 min after inhalation. Lung deposition is homogeneous. Subject started to pedal at beginning of fifth image. Following image shows that radioactivity in lungs has decreased and that radioactivity in kidneys has increased

Exercise

The onset of the exercise was followed by a large and significant ($p < 0.01$) increase of both respiratory rate (29 ± 10 min^{-1}) and heart rate (120 ± min^{-1}) maintained throughout the exercising period.

A striking effect on [^{99m}Tc]DTPA clearance was also observed. The clearance rates of both lungs significantly increased by a factor of 2 ($p < 0.05$) (Table 2). In contrast, no difference was found in the control group between the clearance rates of the lung computed during the twentieth to twenty-seventh minutes after the inhalation. The three-factor analysis showed that this difference between the two groups is due significantly to a regional difference between the evolution of apical and basal clearance rates ($p < 0.001$). In the experimental group, a dramatic increase of the apical clearances was observed: 3.40 ± 0.63% min^{-1} compared with 1.82 ± 0.75% min^{-1} ($n = 7$, $p < 0.01$) with a large variation ranging from 1.25 to five times that number from one subject to another. However, no change of the basal clearance rate was demonstrated (1.40 ± 0.82% min^{-1} at rest compared with 1.46 ± 0.68% min^{-1} at exercise) (Fig. 2). That increased the difference existing at rest between apical and basal clearances, the former being at exercise greater than twofold the latter ($p < 0.001$).

Ventilation per volume ratios computed with ^{81m}Kr increased in the apices (2.4 ± 0.69 min^{-1}) and the bases (2.7 ± 1.07 min^{-1}) compared with the resting period, the percentage of increase being 50% more in the apices than in the bases and the distribution of $\dot{V}/V$ between the apical and basal regions became quite uniform (1:1.1). In the control group, no difference was found between the apical clearance rates computed 7 min after the inhalation and those computed during the twentieth and the twenty-seventh minutes of the study.

DISCUSSION

The aerosol of [^{99m}Tc]DTPA used in this study was made of submicronic dry particles. These particles were completely hydrated in the mouth after inhalation and their diameter did not exceed 2 μ in the subsegmental bronchi and peripheral airways (*13,14*). Thus, they were mainly deposited in the alveoli as can be judged on the serial scintigraphies of Fig. 1 where the bronchial trees are indiscernable.

As the [^{99m}Tc]DTPA contained in the lung is cleared, the background in pulmonary blood volume and chest wall increases and, for this reason, the clearances are usually computed in the first 7 or 10 min

TABLE 1
Heart Rates and Respiratory Rates at Rest and Exercise

Subject no.	Age (yr)	Sex	Heart rate (min^{-1}) I*	Heart rate (min^{-1}) II†	Respiratory rate (min^{-1}) I	Respiratory rate (min^{-1}) II
1	36	M	80	120	14	26
2	32	M	88	91	9	14
3	29	F	90	120	12	44
4	26	M	90	116	10	22
5	34	F	94	118	13	30
6	25	F	108	156	18	40
7	35	F	110	120	13	26
Mean ± s.d.			94 ± 10	120 ± 19	12 ± 3	29 ± 10
p‡				<0.01		<0.01

* I = Rest immediately before the exercise.
† II = Exercise.
‡ p Value obtained comparing values obtained from I and II.

following the inhalation of the aerosol (*4*). The extrapulmonary background is obviously nonhomogenous (large airways, stomach, kidneys) and difficult to evaluate. Nevertheless, the data reported here show that, in control subjects, there was nonsystematic difference between the values computed immediately and those computed 20 min after the inhalation. Moreover, in the experimental group, the count rate in a background ROI, reflecting the extrathoracic background under the lung bases, remained quite constant at rest and increased significantly at exercise. This constancy is easily explained since DTPA is cleared from the blood by the kidneys ten times faster than it enters the blood from the lungs (*15*). Since the background count rate never exceeded 15% of the count rate of the lower lung field and remained constant, it does not significantly modify the general trend of the phenomena observed in the lungs. Therefore we decided, as have others, to overlook it (*16*).

For statistical reasons, the quality of the monoexpo-

TABLE 2
[^{99m}Tc] DTPA Clearance Rates (k)
(% min^{-1})

Subject no.	Age (yr)	Sex	Left lung I*	Left lung II†	Right lung I	Right lung II	Apices I	Apices II	Bases I	Bases II
Experimental										
1	36	M	0.78	1.79	0.74	1.44	1.13	3.12	0.90	0.71
2	32	M	1.20	2.53	2.03	2.19	1.61	3.61	1.74	1.28
3	29	F	1.51	1.81	0.89	1.92	2.02	2.24	1.04	0.84
4	26	M	2.51	3.58	3.09	3.43	3.40	3.95	1.90	2.33
5	34	F	1.76	1.89	2.96	3.13	1.68	3.16	2.89	2.14
6	25	F	1.05	3.05	0.51	4.05	1.20	4.14	0.50	2.12
7	35	F	1.46	2.18	0.76	1.54	1.76	3.62	0.85	0.83
Mean ± s.d.			1.46 ± 0.56	2.4 ± 0.69	1.56 ± 1.1	2.52 ± 1.	1.82 ± 0.75	3.4 ± 0.63	1.40 ± 0.82	1.46 ± 0.71
p‡				<0.05		<0.05		<0.01		N.S.
Control										
8	27	F	0.85	0.67	0.90	0.51	0.71	0.69	0.91	0.80
9	40	F	1.68	1.89	1.63	1.31	1.80	2.83	1.94	1.63
10	29	F	0.76	1.10	0.62	0.82	2.98	1.86	0.35	1.89
11	28	M	0.82	0.75	0.75	0.72	1.57	1.07	0.40	1.02
12	34	F	0.94	0.94	0.96	1.25	2.40	1.36	0.86	1.36
Mean ± s.d.			1.01 ± 0.38	1.07 ± 0.48	0.97 ± 0.39	0.92 ± 0.34	1.89 ± 0.85	1.56 ± 0.82	0.89 ± 0.63	1.34 ± 0.44
p‡				N.S.		N.S.		N.S.		N.S.

* I = First 7 min of resting period.
† II = Exercise for experimental group and interval between twentieth and twenty-seventh min of resting period for control group.
‡ p Value obtained comparing values obtained from I and II.

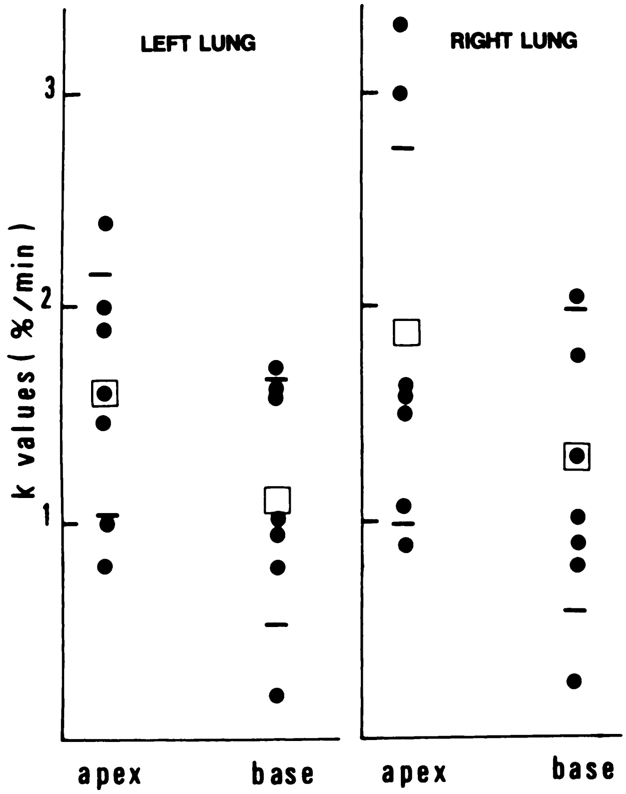

FIGURE 2
Comparison of clearance rate (k) of $[^{99m}Tc]$DTPA in apex and base of each lung. (□) Means; (⊥) s.d. Mean clearance is significantly higher in apices than in bases ($p < 0.05$)

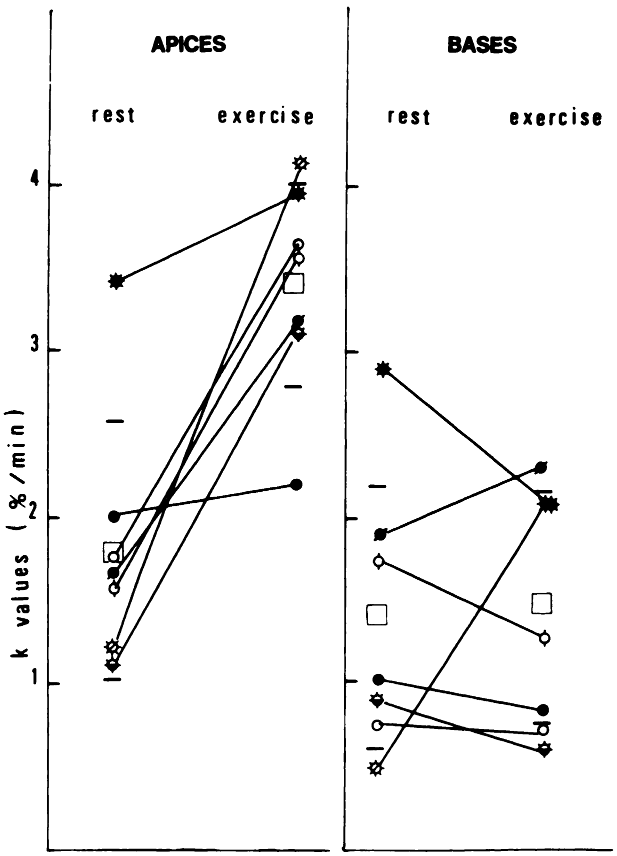

FIGURE 3
Comparison of apical and basal clearance rates (k) of $[^{99m}Tc]$DTPA at rest and exercise in seven subjects. (□) Means; (⊥) s.d. In apices, mean clearance rate is significantly different at exercise from mean at rest ($p < 0.01$)

nential fit depends on the count rate in every ROI and, therefore, we added the count rate of both apices and bases together; no significant difference occurred between left and right lung. With this procedure the correlation coefficients for the best fit monoexponential regression analysis averaged 0.94 ± 0.06.

The results obtained at exercise in this study provide a new finding. Exercise at 50 W, in upright position, causes a doubling of the apical clearance of the $[^{99m}Tc]$DTPA with insignificant changes of the basal clearance. This increase appeared immediately after the onset of exercise; it is probably slightly underestimated since no attempt was made to correct the results from accumulation of radioactivity in chest wall or in pulmonary blood volume which increases in upright exercise (*17*). These results could be explained by three different factors: regional changes in mucociliary clearances, ventilation or perfusion.

The effect of mucociliary clearance on the upper respiratory tract, which may be to increase the clearance of $[^{99m}Tc]$DTPA, can easily be excluded. This mechanism would have resulted in an hilar accumulation of radioactivity which was not observed after the 7-min exercising period.

The effect of the hyperventilation induced by exercise on the alveolar distension must also be discussed. The regional differences of DTPA clearances throughout the lungs have, indeed, been attributed primarily to the regional differences of the degree of alveolar distension (*4*). Experiments on normal subjects or animals placed under positive end-expiratory pressure have supported this explanation (*18*). In addition, we found as reported by others that at rest there is an uneven distribution of the $[^{99m}Tc]$DTPA clearance in normal lungs. The clearance is higher in the apices than in the bases in upright posture, which can be explained in terms of alveolar distension. In the seated subject, there is a gravity-dependent gradient of alveolar volume. Due to regional differences in static transpulmonary pressure, the upper lung regions appear to be relatively more expanded than the lower ones and consequently have a higher clearance.

At exercise we observed some redistribution of the ventilation towards the upper zones of the lungs. The apical ventilation value ratio increased 50% more than the basal one, but this lead to an homogenization of regional ventilation volume ratios throughout the lungs. This is in keeping with the previous reported data from Bryan et al. (*8*). Thus, if alveolar distension was a predominant factor, DTPA clearance should be identical in apices and bases when in our experiment the apical clearance is 2.4 times faster than the basal clearance.

In contrast, the redistribution of pulmonary blood flow towards the upper lung—which is the main change in the regional lung function observed for these levels of exercise—can more easily explain our results. In normal subjects seated at rest, the apices are relatively underperfused. The apical blood flow has been calculated to be five times lower (0.691/min) than the basal blood flow (3.521/min), and it has been demonstrated that a light exercise increases it considerably (*8*). Thus, for the same level of exercise used in this study, Harf et al., using infusion of ^{81m}Kr, found in normal upright subjects a large increase of apical blood flow reaching 150% of rest level (*9*). The rate of increase was rapid and within 40 sec of starting to pedal the maximum level is reached. Little change was observed when the workload was increased to 100W. Bryan et al., using xenon-133, had previously computed, 7 min after the onset of an exercise at 50W, a 160% increase of the perfusion per unit volume in the upper zones of normal seated subjects and a 27% decrease in the lower zones (*8*). Technetium-99m DTPA clearance in animals was dependent on pulmonary blood flow since a total unilateral pulmonary arterial occlusion significantly decreased its value compared with that of a normally perfused lung (*18*). This dependence occurs over a certain range of blood flow since the overperfused, unobstructed lung exhibited no change of its [^{99m}Tc]DTPA clearance (*18*). These results are consistent with our data since at rest in upright posture, the apices of the lung are in zone I conditions at a low pulmonary artery pressure, and a certain number of pulmonary capillaries are closed (*19*). This is a similar condition to the one existing in the occluded pulmonary vascular bed in animals. Indeed, light exercise (50 W) fully recruits this underperfused, pulmonary vascular bed, opening new capillaries as demonstrated by Goresky (*16*). This restores a normal perfusion of the apices which in turn increases the DTPA clearance. Conversely, the bases of the lung are in zone IV conditions at rest (*19*). The capillaries are already recruited and no change is observed at exercise.

Therefore, it can be concluded that the increase of the apical clearance of [^{99m}Tc]DTPA observed with mild exercise without change of basal clearance is primarily due to the increase of apical blood flow demonstrated in these conditions by other investigators (*8,9*).

However, it has been demonstrated that at rest the clearance rate of DTPA is influenced very little by blood flow per se, it being two or three orders of magnitude slower than those found for flow-limited substances like inhaled $C^{15}O_2$ (*20*). It can therefore be suggested that the effect of the increase of apical blood flow on DTPA clearance is indirect and operates through the increase of the permeability surface area product due to the recruitment of new capillaries induced by exercise. The opening of the capillaries at exercise increases the exchange surface offered to the DTPA aerosol and, in turn, the clearance rate. A similar mechanism has been suggested by Braude et al. to explain the increased DTPA clearance observed after an inhalation of histamine which induces a recruitment in the pulmonary arterial bed (*7*). Coates has recently demonstrated in sheep that exercise induced a threefold increase of pulmonary lymphatic flow suggesting an increase in the microvascular surface of the lung (*21*).

Our study suggests that the results of [^{99m}Tc]DTPA clearances observed in the apices cannot be interpreted in patients without taking into account the physiologic or pathologic factors or drugs used that are able to induce an apical redistribution of pulmonary blood flow.

FOOTNOTES

[†] TSI 3030.

[‡] Thompson-CGR, Paris, France (Acticamera).

[§] Sopha Medical, Paris, France (Simis 3).

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