Pulmonary Membrane Diffusing Capacity and Capillary Blood Volume in Tropical Eosinophilia*

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Pulmonary membrane diffusing capacity (Dm) and pulmonary capillary blood volume (Vc) measurements were carried out in 21 patients with untreated tropical eosinophilia and 21 healthy controls matched for age, sex, height, and smoking habit. The mean single breath transfer factor (Dco) and the mean membrane diffusing capacity were significantly lower (p<0.001) in patients with tropical eosinophilia compared with control subjects. However, the mean capillary blood volume was not significantly different (p>0.2). The positive correlations between Dm and transfer factor (r = 0.525), between Dm and effective alveolar volume (Va) (r = 0.721), and between Dco and Va (r = 0.774) were also highly significant (p<0.001) in study patients prior to treatment. These data suggest that reduction in single breath transfer factor in untreated tropical eosinophilia may be due to a reduction in membrane diffusing capacity, which in turn may be due to a reduction in area of membrane available for diffusion, as evidenced by the significantly reduced Va (p<0.001) in these patients. Since pulmonary capillary blood volume was normal, the pulmonary perfusion was within normal limits. Following three weeks of treatment with diethylcarbamazine citrate, although there was a significant rise in single breath transfer factor (p<0.001) and membrane diffusing capacity (p<0.05), both Dco (p<0.01) and Dm (p<0.01) continued to be significantly lower than those of control subjects. However, pulmonary capillary blood volume did not show any change (p>0.2).

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Subjects and Methods

Twenty-one patients with TE with symptoms of less than six months' duration and 21 healthy control subjects, matched for age, sex, height, and smoking habits were studied. The diagnosis of TE was based on the criteria of residence in the filarial endemic area of Madras city, respiratory symptoms such as cough, dyspnea, and nocturnal wheezing, chest roentgenogram infiltrates; peripheral blood eosinophilia with absolute counts of ≥2,000 cells/μm, high serum titers of antifilarial IgG, and a favorable response to diethylcarbamazine citrate. All normal control subjects were of South Indian ethnic origin. None had respiratory symptoms or abnormal physical findings. All had normal chest roentgenograms and normal pulmonary function. None had elevated peripheral blood eosinophil values and none was taking any medication.

All patients were offered diethylcarbamazine citrate 6 mg/kg of body weight per day orally for 21 days and 19 patients consumed the drug regularly. The transfer factor and its subdivisions were repeated at one month in these 19 patients who had completed treatment. Tests could not be repeated in the remaining two patients.

All pulmonary function tests, including single breath carbon monoxide diffusing capacity (Dco), membrane diffusing capacity (Dm), and pulmonary capillary blood volume (Vc) measurements were carried out (Transfer Test Model C, F.K. Morgan Ltd, Chatham, U.K.). All the subjects attended the clinic between 7:30 and 8 AM and the single breath measurements were performed after 12 noon to make sure that none of the smokers had smoked tobacco at least four hours preceding the test. All single breath diffusing capacity measurements in this study were performed by previously reported methods. Initially the single breath Dco and effective alveolar volume (Va) in each subject were determined, in duplicate,
while breathing a mixture of 14 percent helium, 0.288 percent carbon monoxide, 18 percent oxygen, and the remainder nitrogen. The difference between the measurements was less than 5 percent and the highest value was used for analysis. This was followed by the determination of Dm and Vc by performing two single breath Dco measurements at two levels of alveolar oxygen tension: one at the level obtained during breathing oxygen and the other breathing air. First, the subject breathed oxygen for five minutes to raise the alveolar oxygen tension and this is followed by determination of single breath Dco by inhaling a mixture of 14 percent helium, 0.288 percent carbon monoxide, and the remainder oxygen. The subject then breathes air for ten minutes to wash out the remains of previous inspiration from the lungs and performs another single breath Dco maneuver by inhaling a gas mixture of 14 percent helium, 0.288 percent carbon monoxide, 18 percent oxygen, and the remainder nitrogen. (All gas mixtures in this study were provided by P.K. Morgan Ltd, Chatham, U.K.) Hemoglobin which was measured in grams per deciliter, was measured in each subject. The Dm and Vc were then calculated.

We had made serial measurements of Dco, VA, Dm, and Vc in healthy volunteers at monthly intervals. The coefficients of variation for Dco and VA were less than 5 percent and for Dm and Vc they were less than 10 percent.

All data were presented as mean ± SEM. Statistical analysis was performed using two-tailed Student's paired t-test. Correlation and regression coefficients were obtained by the standard linear regression procedure. A p value of <0.05 was considered significant.

RESULTS

All patients with TE and control subjects were male and seven subjects in each category were smokers. The mean (± SEM) age in patients with TE was 24 ± 1.5 years, height was 166.0 ± 1.6 cm, and weight was 74.8 ± 4.8 kg. The mean (± SEM) age in control subjects was 24.0 ± 1.6 years, height was 167.0 ± 1.6 cm, and weight was 51.1 ± 2.0 kg. The hemoglobin level at diagnosis varied from 11.0 to 15.6 g/dl in patients with TE (mean ± SEM, 12.9 ± 0.3 g/dl) and in control subjects it was 11.0 to 16.9 g/dl (mean ± SEM, 13.9 ± 0.3 g/dl), and this difference was just significant statistically (p = 0.04). The mean posttreatment hemoglobin level (13.1 ± 0.3 g/dl) was not significantly different from mean pretreatment level (12.9 ± 0.3 g/dl, p = 0.2) and control values (13.94 ± 0.37 g/dl; p > 0.05) (Table 1).

The single-breath Dco, VA, Dm, and Vc measurements in patients and control subjects are given in Table 1. The mean Dco (TE, 7.0 ± 0.3 mmol/kpa/min; control, 9.4 ± 0.5 mmol/kpa/min; p < 0.001) and mean VA (TE, 3.6 ± 0.2 L; control, 4.4 ± 0.2 L; p < 0.01) were significantly lower in patients with TE compared with control subjects. The mean membrane diffusing capacity was also significantly lower in untreated TE (TE, 9.4 ± 0.6 mmol/kpa/min; control, 13.4 ± 0.6 mmol/kpa/min; p < 0.001). However, the mean pulmonary capillary blood volume was not significantly different from control subjects (TE, 74.8 ± 4.8 ml; control, 78.0 ± 4.5 ml; p > 0.2).

In study patients, before treatment, there was significant correlation between Dm and Dco (r = 0.825, p < 0.001, Fig 1) between Dm and VA (r = 0.721, p < 0.001), and between Dco and VA (r = 0.774, p < 0.001). However, there was no correlation between Vc and Dco (r = −0.086) and between Vc and VA (r = −0.060) (Table 2).

All patients had shown remarkable clinical response to three weeks of treatment with diethylcarbamazine. There was also a significant fall (p < 0.001) in the mean peripheral blood eosinophil value from 11,540 ± 1,389 cells/cu mm (range, 3,100 to 26,475 cells/cu mm) to 2,160 ± 429 cells/cu mm (range, 150 to 7,830 cells/cu mm) following treatment. On comparison with paired observation in 19 patients who had completed treatment successfully, the mean Dco (pretreatment, 6.8 ± 0.4; one month, 7.8 ± 0.4; p < 0.001), the mean VA (pretreatment, 3.7 ± 0.2; one month, 4.0 ± 0.2; p < 0.001), and the mean Dm (pretreatment 9.6 ± 0.6; p < 0.001) were significantly higher than the corresponding values at diagnosis (Table 2).

### Table 1—Transfer Factor and Its Subdivisions in Patients at Diagnosis and Control Subjects (Mean ± SEM)*

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
<th>Patients with TE at Diagnosis</th>
<th>Significance</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(n = 21)</td>
<td>(n = 21)</td>
<td></td>
</tr>
<tr>
<td>Dco, mmol/kpa/min</td>
<td>9.4 ± 0.5</td>
<td>7.0 ± 0.3</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>VA, L</td>
<td>4.4 ± 0.2</td>
<td>3.6 ± 0.2</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Dm, mmol/kpa/min</td>
<td>13.4 ± 0.6</td>
<td>9.4 ± 0.6</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Vc, ml</td>
<td>78.0 ± 4.5</td>
<td>74.8 ± 4.8</td>
<td>NS</td>
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</tbody>
</table>

*NS = not significant; TE = tropical eosinophilia.

### Table 2—Effect of Treatment on Transfer Factor and Its Subdivisions in Patients with Tropical Eosinophilia (TE) (Mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Patients with TE at Diagnosis</th>
<th>Patients with TE at One Month</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(n = 19)</td>
<td>(n = 19)</td>
</tr>
<tr>
<td>Dco, mmol/kpa/min</td>
<td>6.8 ± 0.4</td>
<td>7.8 ± 0.4</td>
</tr>
<tr>
<td>VA, L</td>
<td>3.7 ± 0.2</td>
<td>4.0 ± 0.2</td>
</tr>
<tr>
<td>Dm, mmol/kpa/min</td>
<td>9.6 ± 0.6</td>
<td>11.3 ± 0.7</td>
</tr>
<tr>
<td>Vc, ml</td>
<td>70.2 ± 3.3</td>
<td>73.1 ± 4.5</td>
</tr>
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</table>

*NS = not significant.
one month, 11.3 ± 0.7; p<0.05) had shown a significant rise following treatment (Table 2). However, there was no difference in mean values of Vc following treatment (pretreatment, 70.2 ± 3.3; one month, 73.1 ± 4.5; p>0.2). The mean posttreatment values of Dco, VA, and Dm continued to be significantly lower than those of controls (p<0.01 for each comparison).

**DISCUSSION**

The significant reduction in membrane diffusing capacity without a reduction in pulmonary capillary blood volume suggests that the reduction in Dco in TE may be due mainly to a reduction in membrane diffusing capacity. The significant correlation of Dm with Dco and VA further suggests that the reduction in the area of membrane available for diffusion as evidenced by a significantly reduced VA may be responsible for the lower Dco and Dm in untreated TE. These findings are in agreement with the previous studies of components of the transfer factor in which it had been shown that there is a significant correlation between Dm and VA; and Dco is dependent on lung volume and Dm.7

As our study subjects are not anemic or polycythemic, there may not be any abnormal influence of hemoglobin on Θ.8 Similarly, all smokers in this study were light smokers (smoking less than five cigarettes per day for less than two years) and none had smoked for at least four months preceding the test. Since smoking produces mainly a reduction in pulmonary capillary blood volume,8 the observation of normal pulmonary capillary blood volume in these patients suggests that a mild degree of smoking by a proportion of patients did not influence the results of the study.

A significant reduction in Dm alone, without a reduction in Vc, had been reported in patients with systemic sclerosis without chest roentgenographic changes8 and in patients with submassive pulmonary embolism.10 However, in patients with systemic sclerosis with an evident pulmonary localization as shown by chest roentgenographic changes,9 there was a reduction in both Dm and Vc. Thus, a reduction in both Dm and Vc was observed in patients with systemic sclerosis as the disease progressed to have radiologic localization. The demonstration of degenerating microfilariae in pulmonary parenchyma13 and also the histopathologic observation of mild to moderate thickening of both pulmonary arteries and veins in a patient with a TE with a three-year duration of symptoms14 suggested that there might be changes in pulmonary capillary blood volume that might have contributed to the reduction in Dco. Therefore, a reduction in membrane diffusing capacity alone, without a significant reduction in pulmonary blood volume in our patients with TE with symptoms less than six months’ duration, may suggest that the disease might not have progressed to produce reductions in both Dm and Vc.

The reduction in Dm in our study may be due to the inflammatory changes produced by the abnormally accumulated eosinophils in the lower respiratory tract14 and the eosinophils have been shown to produce toxic mediators injurious to pulmonary parenchyma.15 All our patients had symptoms less than six months’ duration at diagnosis and hence the “injury” that may result from eosinophilic alveolitis12,14,15 may not be severe enough to have any deleterious effect on the pulmonary capillary blood volume, although it had produced a significant reduction in Dm.

There was a remarkable clinical response to a standard three weeks of treatment with diethylcarbamazine citrate and this had resulted in a significant rise in Dco, VA, and Dm. However, these values did not return to normal despite treatment and the reason for the persisting abnormality is not immediately apparent. Since all our study patients had their first episode of TE of less than six months’ duration, the persisting abnormality at one month was not due to the development of some degree of permanent abnormal pulmonary function from a previous episode of this disorder. It has been shown previously that there was a significant reduction in lung eosinophils even with 6 to 12 days of treatment with diethylcarbamazine,16 and there was a significant reduction in peripheral blood eosinophils at one month in this study. The suppression of the eosinophilic inflammatory process12 in the lower respiratory tract, therefore, might have resulted in an improvement in Dco and Dm.

In summary, patients with TE presenting with shorter duration of symptoms at diagnosis (<6 months) had a significant reduction in both Dco and Dm. The pulmonary perfusion was normal, as evidenced by a normal pulmonary capillary blood volume. Thus, the reduction in transfer factor in TE may be due to a reduction in membrane diffusing capacity. Treatment with diethylcarbamazine citrate resulted in a significant improvement in Dco and Dm, but these parameters did not return to normal despite treatment.

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